

IMMUNOBIOLOGY OF NANOMEDICINE: BIOCHEMICAL AND BIOPHYSICAL DETERMINANTS OF NANO-IMMUNE SYSTEM INTERACTIONS

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Abstract

Nanomedicine integrates pharmaceuticals, nanotechnology, and molecular life sciences to enhance therapeutic delivery and diagnostic precision. Engineered nanomaterials enable controlled drug release, improved pharmacokinetics, and targeted interaction with biological systems. Immune recognition remains a critical factor influencing nanoparticle biodistribution, circulation stability, therapeutic efficacy, and immunological safety. Interactions at the nano-bio interface are governed by biochemical and biophysical determinants that regulate molecular adsorption, cellular recognition, and immune signalling processes. This review examines the biochemical, biophysical, genetic, and computational determinants that influence interactions between nanomaterials and immune systems, with emphasis on mechanisms shaping immunological compatibility and nanotherapeutic performance. Relevant literature across pharmaceuticals, nanotechnology, immunobiology, molecular genetics, and bioinformatics was analysed to identify key factors governing nano-immune communication. Evidence highlights the importance of protein corona formation, complement activation, receptor-mediated recognition, and gene regulatory pathways in determining immune responses toward nanomaterials. Biophysical characteristics, including particle size, morphology, surface charge, and mechanical rigidity, strongly influence immune cell interaction and intracellular processing. Computational and systems biology approaches further contribute predictive insight into immune signalling networks associated with nanoparticle exposure. Integration of biochemical, biophysical, and molecular perspectives establishes a mechanistic foundation for rational engineering of nanotherapeutic systems with improved immune compatibility. Continued advancement of nanomedicine requires multidisciplinary strategies that optimise nanoparticle physicochemical properties and targeted delivery performance to enhance therapeutic safety and translational applicability.

Keywords: Nanomedicine, Nano-immune interactions, Protein corona, Nanoparticle physicochemical properties, Immunological compatibility

Introduction

Nanomedicine is one of the areas that has been a transformative field in the pharmaceutical and biomedical sciences due to the combination of nanoscale engineering and therapeutic and diagnostic interventions (Bragazzi, 2019). Nanoparticles, nanocarriers, and engineered nanostructures allow targeted drug delivery, increased bioavailability and higher targeting accuracy, both at the cellular and molecular scale (Eleraky et al., 2020). Well-known types of nanomedicine platforms engaging in clinical pharmacology and translational medicine are polymeric nanoparticles, dendrimers, lipid-polymer hybrids, and inorganic nanomaterials (Hadjidemetriou et al., 2017). The nanometer scale allows controlling drug loading capacity, release kinetics, circulation stability, and tissue targeting efficiency as key structural effects, making nanotechnology one of the primary elements of modern pharmaceuticals and the design of the next generation (Kargozar & Mozafari, 2018). Interactions with the immune system are a determinant that affects the biological destiny of nanomaterials after their exposure to the system (Liu et al., 2022). The immune surveillance reactions are highly swift in assessing foreign structures that get introduced into physiological systems by coordinated actions between innate and adaptive immune components (Gomes et al., 2016). The key factors during the recognition and processing of nanoscale materials include macrophages, dendritic cells, neutrophils, complement proteins, and pattern recognition receptors (Aljabali et al., 2023). The immune response affects the nanoparticle circulation period, tissue biodistribution and cellular uptake, inflammatory signalling and therapeutic efficacy, determining the clinical viability of nanomedicine platforms (Liu et al., 2022).

Nano-biological processes that take place at the nano-bio interface have a significant effect on immune recognition pathways. The adsorption of a biomolecule to the surfaces of nanoparticles results in the creation of an active protein corona that redefines the identity of nanoparticles and changes the perception of the immune system (Palmieri and Caracciolo, 2022). Opsonisation, complement activation, and receptor-mediated cellular internalisation are regulated by interactions between the plasma proteins, lipids, enzymes, and glycoproteins (Westmeier et al., 2018). Molecular binding affinity and immune signalling cascades depend on surface functional groups, ligand conjugation, hydrophobicity, and molecular composition, hence defining nanoparticle recognition in biological systems (Rahmati et al., 2020). Immune responses to nanomaterials are also regulated by biophysical parameters that are linked to the structural and physicochemical aspects (Rahmati et al., 2020). The size of the particle determines the dynamics of renal clearance, phagocytic uptake and lymphatic transport, but the geometry of nanoparticles, such as spherical, rod-shaped, and disk-shaped shapes, impacts cellular internalisation pathways and membrane interaction patterns (Moyano et al., 2016). Surface charge distribution controls the electrostatic interactions of proteins with cellular membranes, plasma proteins, and extracellular matrices. Nanoparticle deformation and interaction with biological barriers are also affected by mechanical rigidity and structural elasticity, which have a collective effect on nano-immune communication (Rahmati et al., 2020). Nano-immune interactions are further complicated by molecular regulatory interactions. NOD-like receptors, scavenger receptors, and toll-like receptors are pattern recognition receptors that sense structural motifs of nanomaterials or nanoparticle-bound biomolecules and trigger transcriptional signalling cascades, which control cytokine production, inflammatory responses and immune cell activation (Aljabali et al., 2023). Exposure to nanoparticles might also regulate gene transcription via oxidative stress, apoptosis, antigen presentation, and immune regulation, indicating the influence of molecular and genetic factors in immune responses to nanostructures (Gomes et al., 2016). The accelerated growth in nanomedicine, in both therapeutic, diagnostic and vaccine development settings, has further catalysed the need to learn the immune compatibility of engineered nanomaterials (Sengupta et al., 2022). Nanoparticles, in terms of synthesis, functionalization of the surface and application in targeted drug delivery, have made huge advancements. The mechanistic insight into immune recognition mechanisms, the determinants of immunotoxicity, and the biological responses in the long run have not been fully elucidated (Aljabali et al., 2023). Diversity in the physicochemical properties of nanoparticles, in biological micro-environment and in host immune systems provides irregular performance across experimental systems. There are multidisciplinary approaches that have been integrated in the fields of pharmaceuticals, immunobiology, molecular genetics, nanotechnology, biophysics, and computational sciences, which have prospects of elucidating mechanisms that regulate nano-immune communication. The use of sophisticated analytical methods, multi-omics profiling, computational modelling and high-resolution imaging promotes further research of nanoparticle behaviour in multi-complex biological systems. Additional comparative biological insights and ecological exposure provide further knowledge on biological response to engineered nanomaterials in different species and in different environmental systems (Westmeier et al., 2018). The rational design of immunologically compatible nanomedicine platforms can be supported with the help of a comprehensive synthesis of these perspectives, allowing to attain higher therapeutic safety and efficacy.

The present review examines biochemical, biophysical, and genetic determinants that regulate interactions between engineered nanomaterials and the immune system. Emphasis is placed on molecular recognition mechanisms, physicochemical design parameters, and computational approaches that inform the development of immunologically optimised nanomedicine platforms. Integration of multidisciplinary insights aims to clarify the mechanistic foundations guiding safe and effective nano-therapeutic design.

Review

Nanomedicine Platforms and Pharmaceutical Design Principles

Nanomedicine involves a combination of nanoscale engineering and pharmaceutical formulation approaches with the aim of enhancing therapeutic delivery and pharmacokinetic control as well as molecular targeting (Bragazzi, 2019).

Nanocarrier systems offer structural platforms that can entrap small molecules, biologics, nucleic acids and imaging agents within architectures designed at the nanometer scale (Girdhar et al., 2018). Biodistribution, drugs and cellular internalisation can be modulated by exploiting structural versatility as well as tunable physicochemical properties and controlled surface functionalization (Rahmati et al., 2020). These properties make nanotechnology a very essential ingredient in high-technology pharmaceuticals and targeted therapy (Kargozar & Mozafari, 2018). One of the oldest nanocarriers that has been translated clinically is liposomes (Mishra et al., 2019). Phospholipid bilayer vesicles are used to carry hydrophilic and hydrophobic therapeutic agents in either aqueous cores or a lipid membrane (Chamundeeswari et al., 2019). The systemic stability and duration of circulation depend on membrane fluidity, lipid makeup, and surface modification measures, e.g. the coating of membranes with polyethylene glycol (Wang et al., 2019). The improved permeability and retention in pathological tissues make passive targeting possible in oncology and inflammatory disorders (Eleraky et al., 2020).

Another platform that is extensively studied in the pharmaceutical nanotechnology is polymeric nanoparticles (Mishra et al., 2019). Biodegradable polymers such as poly(lactic-co-glycolic acid), chitosan and polycaprolactone give structural matrices which control the efficiency of drug encapsulation and kinetics of sustained release (Chamundeeswari et al., 2019). Pattern of drug liberation and performance of intracellular delivery is determined by polymer architecture, molecular weight distribution and degradation rates (Subrizi et al., 2019). Surface ligand conjugation promotes uptake through receptor mediated uptake in immune and non-immune populations of cells (Gomes et al., 2016). Dendrimers are macromolecules that have very branched structures with symmetrical architecture and several functional groups on their terminal ends (Mishra et al., 2019). The uniform size of the particles is produced by controlled synthesis and high surface functionality, which allows precise conjugation of drugs and also allows multivalent interactions with biological targets (Wang et al., 2019). Terminal groups are adjustable to control solubility, charge properties, and immunological compatibility in physiological conditions (Rahmati et al., 2020).

The inorganic nanomaterials offer unique physicochemical attributes that broaden the functional abilities of nanomedicine (Aljabali et al., 2023). Gold nanoparticles, silica nanoparticles, magnetic nanoparticles, and quantum dots have optical, magnetic, or catalytic characteristics that can be used to perform diagnostic imaging, photothermal therapy, and biosensing (Sengupta et al., 2022). Surface chemistry engineering allows bioconjugation of peptides, antibodies or nucleic acids with greater biological specificity and therapeutic precision (Moyano et al., 2016). The principles used in designing pharmaceutical design of nanocarrier systems are optimisation of particle size distribution, surface charge, structural stability, as well as drug loading capacity (Rahmati et al., 2020). The size of particles determines clearance by the kidney, uptake by macrophages and tissue penetration (Gomes et al., 2016). Surface chemistry regulates the adsorption and patterns of immune recognition of proteins in biological fluids (Palmieri & Caracciolo, 2022). Drug stability and release kinetics in physiological conditions are controlled by encapsulation approaches such as matrix entrapment, covalent conjugation and electrostatic complexation (Askarizadeh et al., 2023). The combination of these parameters can be used to develop nanomedicine formulations with rational development and increased therapeutic efficacy and immunological compatibility (Hadjidemetriou et al., 2017). Table 1 summarises major nanocarrier systems and their pharmaceutical design characteristics.

Table 1: Major nanomedicine platforms and key pharmaceutical design attributes

Nanocarrier Platform	Structural Composition	Typical Size Range (nm)	Drug Loading Strategy	Pharmaceutical Advantages	Key Reference
Liposomes	Phospholipid bilayer vesicles	50-200	Encapsulation within an aqueous core or a lipid membrane	Biocompatibility, dual hydrophilic-hydrophobic drug loading	(Mishra et al., 2019)
Polymeric Nanoparticles	Biodegradable polymers such as PLGA or PCL	100-300	Matrix entrapment or polymer-drug conjugation	Controlled release kinetics and structural stability	(Chamundeeswari et al., 2019)
Dendrimers	Branched macromolecular polymers with terminal functional groups	5-20	Surface conjugation or internal cavity encapsulation	High drug loading capacity and molecular precision	(Mishra et al., 2019)
Gold Nanoparticles	Metallic Au nanostructures	10-100	Surface adsorption or ligand conjugation	Optical properties and photothermal therapeutic capability	(Sengupta et al., 2022)
Silica Nanoparticles	Porous SiO ₂ nanostructures	50-200	Pore entrapment and surface functionalization	High surface area and tunable pore architecture	(Aljabali et al., 2023)

Biochemical Determinants of Nano-Immune Recognition

The immune recognition mechanisms of nanoparticles at the initial stages of entry into physiological environments are largely mediated by biochemical processes occurring at the nano-bio interface (Liu et al., 2022). Rapid adsorption of

plasma proteins, lipids, and glycoproteins onto nanoparticle surfaces forms a biomolecular layer commonly referred to as the protein corona (Nienhaus & Nienhaus, 2023). This dynamic corona alters the physicochemical identity of nanomaterials and determines subsequent biological interactions with immune components (Palmieri & Caracciolo, 2022). The corona composition is determined by the surface chemistry of nanoparticles, hydrophobicity, charge properties, and the composition of the biological fluid around them (Bilardo et al., 2022). The most common dominant corona constituents that undergo cellular recognition mechanisms are often albumin, immunoglobulins, fibrinogen, complement proteins, and apolipoproteins (Westmeier et al., 2018). Surface chemistry is one of the fundamental determinants that dictate the interactions between nanoparticles and immune cells based on ligand-receptor interaction (Moyano et al., 2016). Hydroxyl, carboxyl, amine, and thiol functional groups have an effect on molecular affinity to membrane receptors on macrophages, dendritic cells, and neutrophils (Rahmati et al., 2020). Pattern recognition receptors and scavenger receptors recognise specific surface ligands, such as peptides, antibodies or carbohydrate motifs (Aljabali et al., 2023). These kinds of molecular interactions control the uptake of nanoparticles by receptor-mediated endocytosis and phagocytosis and, therefore, affect immune activation or immune tolerance based on the molecular architecture of the surface (Gomes et al., 2016).

The other important biochemical prerequisite of nano-immune communication is the activation of the complement system (Freeley et al., 2016). The interaction of complement proteins with surface nanoparticles leads to the activation of enzymatic cascades related to classical, lectin, or alternative complement (Reis et al., 2019). Activation product of complement increases the processes of opsonisation, recruitment of immune cells, and inflammatory reactions in biological tissues (Hess & Kemper, 2016). Complement activation potential is highly sensitive to surface properties like the density of charge, hydrophobic areas, and molecular structures (Liu et al., 2022). Enzymatic activities also control the process of nanoparticle processing in the immune environment (Gomes et al., 2016). There are enzymes, such as esterases, proteases, and oxidative enzymes, which are involved in nanomaterial coating and polymer matrix degradation or modification. These biochemical changes have an impact on nanoparticles' stability, surface composition and biological survival. Immune cells' metabolism also helps in the dynamics of intracellular trafficking and alteration of immune signalling pathways (Aljabali et al., 2023). All these biochemical determinants determine the molecular structure within which nanomaterials interact with host immune surveillance systems. Figure 1 shows the key biochemical pathways during nanoparticle-immune interactions, such as protein corona formation, ligand-receptor binding, complement activation, enzymatic modification, and intracellular trafficking.

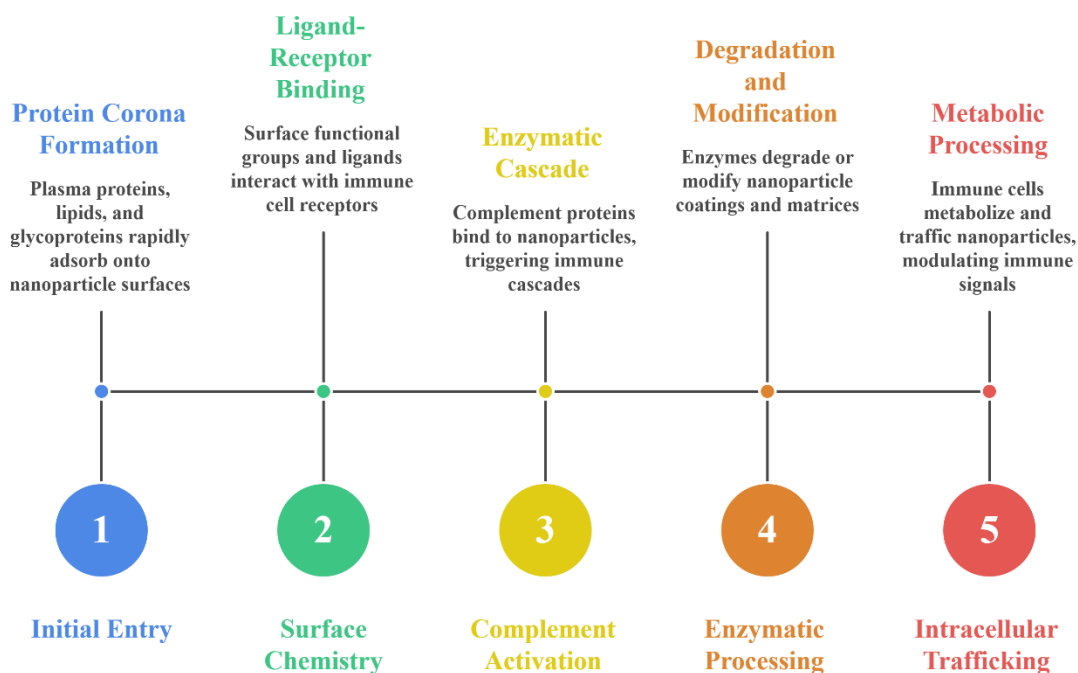


Figure 1: Biochemical mechanisms governing nanoparticle-immune system interactions

Biophysical Properties Governing Nano-Immune Interactions

Interactions between engineered nanomaterials and immune cells, biological barriers, and circulating biomolecules depend on the biophysical properties of engineered nanomaterials (Wang et al., 2022). Structural parameters of nanoparticle size, geometry, surface charge, and mechanical stiffness define the physicochemical behaviour of nanoparticles in physiological environments (Rahmati et al., 2020). These parameters have an impact on the dynamics of circulation, cellular uptake processes, and immune recognition in complicated biological systems (Liu et al., 2022). Particle size is one of the primary factors that have an impact on biodistribution and immune surveillance (Gomes et al., 2016). Nanoparticles in smaller size regimes stay longer in circulation, and the large size structures are immediately eliminated by macrophages' phagocytic activity in organs like the liver and spleen (Aljabali et al., 2023). The lymphatic

transport and interaction with antigen-presenting cells also depend on the size variation (Wang et al., 2019). Particle geometry and topography also further regulate immune cell internalisation pathways (Moyano et al., 2016). The endocytosis of the spherical nanoparticles is usually efficiently achieved, and the structures of rods and filaments have altered dynamics of membrane wrapping and decreased phagocytic uptake (Froimchuk et al., 2021). The surface topographic characteristics, roughness, and nanoscale structures change the protein adsorption patterns and receptor interactions at the cellular interface (Bilardo et al., 2022).

The charge distribution of the surface helps in the electrostatic interaction between nanoparticles and the biological membranes (Rahmati et al., 2020). Plasma proteins and negatively charged cellular membranes exhibit increased association with positively charged nanomaterials and result in better cellular uptake and possible immune activation (Palmieri & Caracciolo, 2022). Both NPs with a neutral or slightly negative surface potential are less prone to nonspecific interactions and have a high circulation stability (Liu et al., 2022). Mechanical rigidity and structural elasticity also determine nanoparticle behaviour in the immune microenvironment (Froimchuk et al., 2021). The flexibility or deformability of nanostructures will increase biological compatibility because they can conform to cellular membranes and physiological obstacles (Wang et al., 2022). Elastic properties control the intracellular trafficking, endosomal escape, and dynamics of interaction with immune cells. Nanoparticle persistence and dynamic behaviour in a physiological environment are eventually determined by thermodynamic stability and interfacial energy (Rahmati et al., 2020). Table 2 presents significant biophysical parameters of nanoparticles and attributes that determine the result of immune interaction in biological systems.

Table 2: Biophysical parameters influencing nano-immune interactions

Biophysical Parameter	Nanoparticle Characteristic	Immune Interaction Outcome	Representative Nanomaterials	Key Reference
Particle Size	10-200 nm diameter	Influences phagocytosis and lymphatic transport	AuNPs, LNPs	(Gomes et al., 2016)
Particle Shape	Spherical, rod, filamentous	Alters membrane wrapping and cellular uptake	CNTs, AuNRs	(Moyano et al., 2016)
Surface Charge	Positive, neutral, negative potential	Controls electrostatic interaction with immune cells	PLGA NPs	(Rahmati et al., 2020)
Mechanical Rigidity	Rigid or deformable structure	Affects intracellular trafficking and cellular compatibility	Liposomes	(Froimchuk et al., 2021)
Surface Topography	Smooth or rough nanoscale architecture	Regulates protein adsorption and receptor engagement	SiNPs	(Bilardo et al., 2022)

Molecular Genetics of Immune Responses to Nanomaterials

Molecular genetic mechanisms that take place in immunologic settings regulate cellular recognition and signalling responses induced by engineered nanomaterials (Aljabali et al., 2023). The activation of innate immune pathways that identify foreign structures that get into biological systems is controlled by signalling networks that are genetically regulated (Alsaleh & Brown, 2018). Immune cells have various receptor families that can detect molecular patterns containing nanoscale material as well as biomolecules adsorbed onto the surface of nanoparticles (Engin et al., 2017). The early immune sensing events and effects downstream of these receptors are orchestrated by genetic regulatory networks that regulate these receptors (Del Giudice et al., 2023). Pattern recognition receptors are used as a basic part of immune genetic surveillance (Alsaleh and Brown, 2018). Receptor families, such as toll-like receptors, nucleotide-binding oligomerisation domain receptors and scavenger receptors, identify structural motifs that are linked to nanomaterials or nanoparticle-bound biomolecules (Liu et al., 2022). The stimulation of these receptors triggers intracellular signalling cascades that also involve adaptor proteins and transcription factors, and kinase pathways (Engin et al., 2017). These signal transduction cascades in turn control the expression of genes that deal with cytokine production, chemokine signalling, and antigen presentation (Gazzi et al., 2020). These transcriptional programs control the recruitment of immune cells, processes of cellular activation, and interactions of the innate and adaptive immune compartments (Aljabali et al., 2023).

Nanomaterials also cause changes in gene expression patterns of immune and non-immune cells with exposure to them (Del Giudice et al., 2023). Nanoparticle internalisation interferes with cellular homeostasis via oxidative stress-related, metabolic adaptation-related and inflammatory signalling processes (Gomes et al., 2016). These biological reactions affect transcriptional control of the immune defence, apoptosis, and cellular stress responses related genes (Alijagic et al., 2020). The profiles of reaction to nanomaterial exposure based on the associated changes in gene expression can establish immune-activation, immune-tolerance, or cellular-adaptation (Westmeier et al., 2018). Epigenetic processes are another control level of nano-immune interaction (Del Giudice et al., 2023). The immune-related genes have DNA methylation patterns, histone modifications, and chromatin remodelling, facilitating access to transcriptional machinery (Engin et al., 2017). The exposure to nanomaterials can cause long-term gene expression changes in immune cells without affecting DNA sequences by epigenetic alterations (Alijagic et al., 2020). Long-term cellular adaptation, immune memory-like

behaviour and long-term responses to nanoscale stimuli are some of the outcomes of such regulatory processes. A combination of molecular genetics and nanotechnology offers an important understanding of the biological compatibility and immunological effects of exposure to engineered nanomaterials (Alsaleh and Brown, 2018).

Bioinformatics and Systems Biology Approaches in Nano-Immunology

The field of bioinformatics and systems biology has provided opportunities to understand nano-immune interactions in their complexity through integration of large-scale biological datasets with computational modelling approaches (Del Giudice et al., 2023). Exposure to nanomaterials induces multifaceted molecular responses, including transcriptomic regulation, proteomic remodelling, and metabolic adaptation across immune cell populations (Aljabali et al., 2023). Analytical platforms capable of integrating multi-omics datasets provide deeper insight into molecular pathways governing immune recognition, inflammatory signalling, and cellular adaptation following nanoparticle exposure (Li et al., 2022). Multi-omics approaches represent a key strategy for characterising molecular responses to engineered nanomaterials (Del Giudice et al., 2023). Transcriptomic profiling identifies gene expression patterns associated with immune activation, cytokine production, oxidative stress responses, and cellular defence mechanisms (Wang et al., 2019). Proteomic studies show that there are changes in the abundance of proteins, signalling pathways, and receptorization associated with the recognition of nanoparticles and their processing by the cell (Engin et al., 2017). Metabolomic analyses also indicate metabolic remodelling that can be linked to immune responses and cellular stresses that result as a response to nanoparticle exposure (Gomes et al., 2016). A combination of the datasets allows building immunological responses to nanoscale materials in the form of detailed molecular landscapes (Li et al., 2022).

Pathway and network analysis of complex datasets can be performed with the help of systems biology frameworks (Palshikar et al., 2022). The computational algorithms are used to map molecular interactions between genes, proteins, and signalling molecules that are related to immune regulation (Katagiri, 2018). The network topology analysis can be used to determine central regulatory nodes affecting the immune activation or tolerance to nanomaterials (Wang et al., 2019). Dynamic pathway modelling also allows simulating immune signalling responses under various nanoparticle physicochemical conditions (Palshikar et al., 2022). Machine learning solutions offer other capabilities of analysis in nano-immunology (Li et al., 2022). Classification of nanoparticle immunogenicity, cytotoxicity, and inflammatory potential is possible by predictive models, which are trained on experimental datasets (Wang et al., 2022). Random forest, support vector machines, and neural networks are examples of algorithms that are used to assess the connection between nanoparticle physicochemical properties and biological reactions (Wang et al., 2019). These models can help determine the primary determinants that have an impact on the immune compatibility of nanomaterials (Li et al., 2022).

Nanomedicine systems are also further rationalised with the help of computational design platforms (Li et al., 2022). Nanoparticle size distribution, functionalization patterns on the surface, and molecular interaction patterns are simulated before the development of an experiment (Engin et al., 2017). By incorporating bioinformatics, predictive modelling and nanotechnology, data-driven design strategies to enhance the therapeutic efficacy and immunological safety of nanomedicine platforms can be realised (Aljabali et al., 2023). Table 3 presents significant computational and systems biology methods to study nano-immune interactions by combining multi-omics data and predictive modelling models.

Table 3: Computational approaches used in nano-immunology

Computational Approach	Data Type Analysed	Analytical Objective	Example Applications	Key Reference
Transcriptomic Analysis	Gene expression datasets	Identification of immune response pathways	Immune activation profiling	(Del Giudice et al., 2023)
Proteomic Profiling	Protein abundance and signalling networks	Mapping nanoparticle-induced signalling changes	Receptor interaction analysis	(Engin et al., 2017)
Metabolomic Analysis	Cellular metabolic intermediates	Detection of metabolic stress responses	Immune metabolic adaptation	(Gomes et al., 2016)
Machine Learning Models	Integrated biological and physicochemical datasets	Prediction of immunogenicity and toxicity	Nanoparticle safety assessment	(Li et al., 2022)
Systems Network Modelling	Multi-omics interaction networks	Identification of regulatory immune nodes	Pathway simulation of nano-immune signalling	(Palshikar et al., 2022)

Comparative and Translational Insights from Zoological Models

The zoological models serve as basic biological systems to assess nano-immune interactions in the controlled physiological environment (Bolker, 2019). The use of experimental animals can be used to carefully study nanoparticle biodistribution, immune activation, and tissue responses in a wide range of different vertebrate immune architectures (Aljabali et al., 2023). Comparative immunology provides an understanding of the conserved immunology in relation to immune responses to nanoscale foreign material (Dougherty and Papin, 2020). Vertebrate organisms have very basic innate immune elements such as phagocytic cells, complement proteins, and pattern recognition receptors, which are

involved in the recognition and clearance of engineered nanomaterials (Alsaleh and Brown, 2018). The rodent models continue to be widely utilised to study the pharmacokinetics, immunogenicity, and inflammatory responses of nanoparticles (Liu et al., 2022). The cellular and molecular pathways are well-characterised in murine immune systems that would enable the use of mechanistic investigation to nano-bio interactions (Engin et al., 2017). Macrophage activation, dendritic cell signalling, and cytokine secretion patterns noted in murine systems are insightful in the understanding of immune surveillance measures that result when nanomaterials are exposed (Gomes et al., 2016). Rodent-based genetic manipulation technologies can be used to study immune signalling pathways that are linked with nanoparticle recognition (Del Giudice et al., 2023). Zebrafish models have some more benefits in the nano-immunology studies (Liegertová & Janoušková, 2023). It is an optical transparency at the initial stages of development that allows visualising the distribution of nanoparticles and the migration of immune cells in living beings (Alijagic et al., 2020). The innate immune system components of zebrafish are functionally similar to those of the mammalian immune system, which enables the assessment of inflammatory and nanoparticle clearance processes (Milani and Ghiselli, 2020). High-throughput screening of nanomaterial toxicity and immune compatibility can be done quickly and with high reproductive capacity (Liegertová and Janoušková, 2023).

Models based on nonhuman primates show more physiological and immunological similarities to human systems (Bolker, 2019). Primates have complex immune regulation, systemic immune responses, and lymphoid tissue organisation, which could be a useful translational finding in the development of clinical nanomedicine (Aljabali et al., 2023). The findings of these types of models help in the study of immune tolerance, nanoparticle pharmacokinetics, and safety profiles under conditions that are close to human physiology (Liu et al., 2022). The comparative study across zoological systems can improve the knowledge about the preserved immune reactions and the species-specific changes in the nanomaterial perception (Dougherty and Papin, 2020). The knowledge is used to translate experimental evidence to develop safe and effective nanomedicine products to treat patients (Li et al., 2022). Figure 2 shows significant zoological models such as rodent, zebrafish and nonhuman primate systems used to study immune responses and biological modifications related to the exposure of nanoparticles.

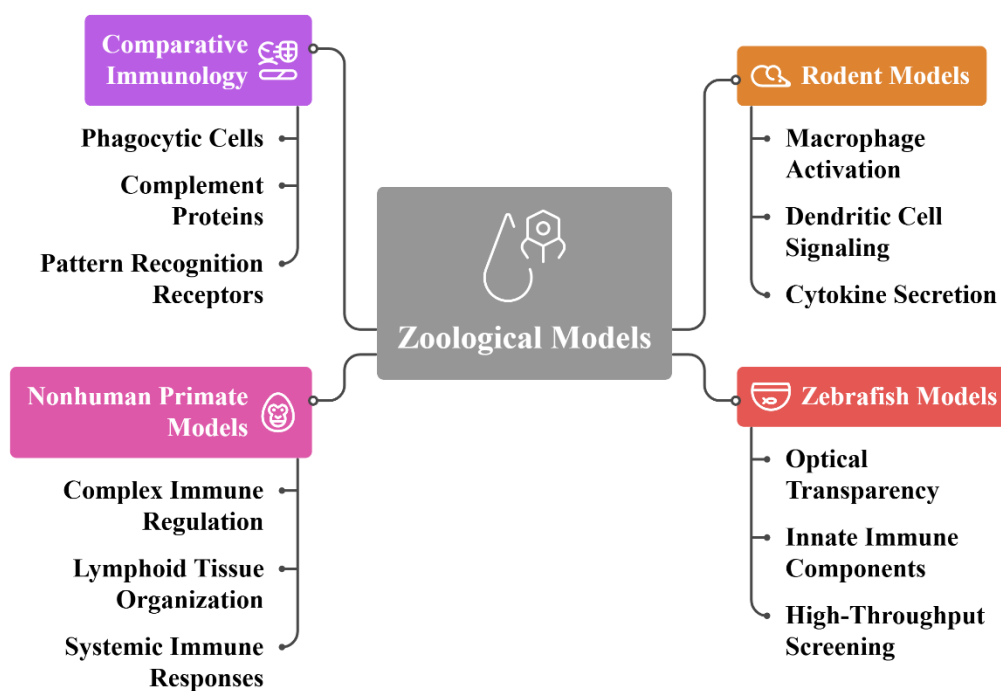


Figure 2: Zoological model systems used for investigating nano-immune interactions

Ecological and Environmental Dimensions of Nano-Immune Interactions

Nanotechnology development in pharmaceutical, industrial, and biomedical industries has increased the environmental emission of engineered nanomaterials into natural environments (Bragazzi, 2019). Nanoparticles produced during the manufacturing process, biomedical waste, agricultural usage, and consumer goods are released into water and soil as a result of wastewater discharge, atmospheric deposition, and soil contamination (Kargozar and Mozafari, 2018). The opportunities for interactions between nanoscale materials and biological systems at various ecological levels are ensured by the persistence of these materials in the environmental matrices (Pinsino et al., 2020). The exposure conditions also present possible immune modulation in the organisms that live in the impacted ecosystems (Alsaleh and Brown, 2018). Aquatic environments are a significant environmental unit that is subjected to engineered nanomaterials (Rong et al., 2021). In water bodies, suspended nanoparticles come into contact with microorganisms, planktic organisms, fish and benthic species (Alijagic et al., 2020). The immune defence mechanisms of these organisms react to foreign

nanoparticles by innate immune responses that include phagocytic responses, antimicrobial peptides production, and antioxidant stress responses (Gomes et al., 2016). Immunological pathway changes have effects on organism health, exposure to pathogenicity, and aquatic population stability (Abimbola et al., 2023).

The deposition of nanoparticles to the terrestrial ecosystems also occurs through deposition in soils and agricultural use (Westmeier et al., 2018). Nanomaterials enter soil invertebrates, plants, and microbial communities by being absorbed via roots and exposed to the microenvironment (Katagiri, 2018). Oxidative stress activation, antimicrobial compounds synthesis, and cellular detoxification are some of the immune-like defence mechanisms of plants and invertebrates (Alijagic et al., 2020). Depending on the composition of nanoparticles and concentration in the environment, biological responses to nanoparticle exposure have the potential to cause ecological changes and physiological disruptions (Pinsino et al., 2020).

Another ecological process related to nanoscale materials is bioaccumulation and trophic transfer (Ranjha et al., 2022). Nanoparticles that are consumed by microorganisms or primary consumers can be spread to trophic levels by predating food webs (Rong et al., 2021). Temporal accumulation in tissues may also have an impact on immune competence, metabolic stability, and survival of an organism in ecological hierarchies (Pinsino et al., 2020). Ecological risk assessment systems are approaches that assess the environmental safety of engineered nanomaterials by jointly examining exposure routes and biological reaction and ecosystem stability (Alsaleh and Brown, 2018). The screening of toxicology, biomarker analysis, and monitoring of the environment make it possible to find long-term ecological implications of the growing range of nanotechnology (Pinsino et al., 2020). Responsible nanomaterials development is achieved through integration of ecological immunology and nanotoxicology into the sustainability of the environment and its ecosystems (Li et al., 2022).

Immunological Engineering of Nanotherapeutics

Nanotherapeutics are a novel form of nanotechnology, immunobiology, and pharmaceuticals that are used to control immune reactions in a highly precise manner (Jiang et al., 2017). Engineered nanomaterials can be used as carriers, as immune-targeting constructs or adjuvant platforms that have the potential to regulate immune cell behaviour, antigen presentation or cytokine signalling pathways (Li et al., 2020). Selective interaction with one or more immune cell populations, such as dendritic cells, macrophages, B lymphocytes and T lymphocytes, is made possible by structural customisation of nanocarriers (Song et al., 2020). The immune receptor recognition and immune communications are regulated through the surface functionalization strategies where antibodies, peptides, carbohydrates, or nucleic acid ligands are incorporated (Moyano et al., 2016). Nanovaccine platforms represent a prominent application of immunologically engineered nanomaterials (Sengupta et al., 2022). Nanoscale carriers allow efficient co-delivery of antigens and immunostimulatory molecules within a single structural framework (Jiang et al., 2017). Encapsulation of protein antigens, messenger RNA, peptide antigens, or epitopes within lipid or polymeric nanoparticles improves antigen stability and promotes uptake by antigen-presenting cells (Zheng et al., 2021). Enhanced antigen processing supports stronger activation of lymphocytes and long-term immunological memory formation (Song et al., 2020).

Immunomodulatory nanomaterials also provide strategies for regulating inflammatory signalling pathways associated with autoimmune disorders, infectious diseases, and cancer immunotherapy (Li et al., 2022). Surface chemistry modification or therapeutic loading with immunosuppressive or immunostimulatory molecules enables modulation of cytokine secretion, macrophage polarisation, and lymphocyte activation (Jiang et al., 2017). Controlled release properties and targeted delivery approaches reduce systemic toxicity and improve therapeutic specificity within immune tissues (Schrijver et al., 2021). Targeted delivery strategies further enhance nanotherapeutic performance through selective accumulation in lymphoid organs such as lymph nodes, spleen, and bone marrow (Zheng et al., 2021). Optimisation of nanoparticle size, ligand-mediated targeting, and biodegradable material design facilitates efficient entry into immune compartments that coordinate antigen presentation and immune signalling (Li et al., 2020). Advances in precision nanomedicine support the development of personalised immunotherapeutic systems guided by molecular biomarkers and genetic profiling (Song et al., 2020). Integration of immunological engineering and nanotechnology enables rational design of therapeutic platforms capable of directing immune responses toward disease-specific molecular targets within complex biological environments (Li et al., 2022).

Conclusion

The interactions between engineered nanomaterials and immune systems can only be well understood through a combination of biochemical, biophysical, and molecular determinants that work together to control the nano- bio interface. Physicochemical properties of nanoparticles, such as surface chemistry, particle size, charge distribution, structural morphology and mechanical properties control protein corona formation, receptor-mediated recognition, internalisation by cells and downstream immunological signalling. The biochemical mechanisms related to complement and activation, biomolecular adsorption, and enzymatic modification also define the nanoparticle identity in the biological fluids and determine immune compatibility. The further complications are added by genetic and transcriptional regulation mechanisms involving the activation of pattern recognition receptors, cytokine signalling cascades, as well as immune regulation pathways that regulate inflammatory responses and cellular adaptation. The systematic analysis of nano-immune communication in complex biological systems can be achieved through the application of multidisciplinary modes of analysis in pharmaceuticals, nanotechnology, molecular genetics, biophysics and bioinformatics. The knowledge of the behaviour of nanomaterials in different organisms and under different environmental conditions is complemented

by related observations that are conducted with the assistance of zoological models and ecological studies. It is on this basis of integrative knowledge that principles of rational engineering of nanotherapeutic systems can be developed so as to achieve controlled immune engagement with improved safety profiles. Future developments in immunologically-sophisticated nanomedicine constructs necessitate the precise control of nanoparticle physicochemical traits, elaborate computational modelling strategies and the target delivery technologies that all enhance therapeutic potential, biological compatibility, and translational applicability in modern biomedical practice.

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