

Nanoparticles and Their Applications in Biology: Synthesis, Nano–Bio Interactions, Biomedical Applications, Toxicity and Future PerspectivesRajasekhar Chikati^{*1}, B. Vigneshwara Reddy², Bonala Kalyana Chakravarthy³, SN Meeravali⁴¹ Department of Biochemistry, Yogi Vemana University, Kadapa, Andhra Pradesh–516005^{2&3} Department of Biotechnology, Yogi Vemana University, Kadapa, Andhra Pradesh – 516005,⁴Department of Botany, Yogi Vemana University, Kadapa, Andhra Pradesh – 516005

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Nanoparticles have emerged as versatile platforms at the interface of materials science and biology because their small dimensions, high surface-area-to-volume ratio, tunable surface chemistry and size-dependent optical, magnetic and electronic properties permit interactions with biomolecules and cells that are difficult to achieve with bulk materials. This review summarizes the state of knowledge available through December 2012 on the classification and synthesis of biologically relevant nanoparticles, their interactions with biological systems, major biomedical applications, and the principal concerns surrounding biocompatibility and safety. Metallic, metal-oxide, magnetic, polymeric, lipid-based and semiconductor nanoparticles are discussed together with conventional physicochemical fabrication and biological or “green” synthesis using microorganisms and other biological systems. Particular attention is given to the nano–bio interface. In physiological fluids, nanoparticles rapidly adsorb proteins and other biomolecules, forming a corona that can alter their biological identity, cellular uptake, biodistribution, targeting and toxicity. Biomedical applications include drug and gene delivery, cancer therapy, diagnostic imaging, biosensing, magnetic separation and combined diagnostic–therapeutic approaches. Despite substantial promise, translation is constrained by variable physicochemical properties, aggregation, dose-dependent toxicity, oxidative stress, inflammatory responses, uncertain long-term fate, manufacturing reproducibility and the need for standardized characterization and risk assessment. The evidence available by 2012 indicates that biological performance cannot be predicted from composition alone; size, shape, surface charge, coating, dose, exposure route and the surrounding biological environment must be considered together. Future progress therefore depends on reproducible synthesis, rigorous nano–bio characterization and safety-by-design strategies that integrate therapeutic performance with biocompatibility.

Keywords: Nanoparticles, nanobiotechnology, nanomedicine, biological synthesis, protein corona, drug delivery, nanotoxicology.

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**1. Introduction**

Nanotechnology has created a framework for engineering materials at dimensions comparable with proteins, membranes, viruses and intracellular structures. Nanoparticles are commonly discussed within the approximately 1–100 nm scale, although biomedical nanocarriers may extend beyond this range depending on composition and application. At these dimensions, a large fraction of atoms or functional groups can be located at the particle surface, and quantum, optical, magnetic and interfacial effects may become prominent. Consequently, nanoparticles can be engineered to carry drugs, bind biomolecules, generate imaging contrast, respond to external fields or interact selectively with cells. The biological usefulness of nanoparticles is closely linked to controllable physicochemical properties. Particle diameter influences circulation, diffusion and cellular internalization; shape can affect contact with membranes and uptake; surface charge influences colloidal stability and interactions with proteins; and surface ligands can provide steric stabilization or molecular recognition. These features created strong interest in nanomedicine, particularly for drug delivery, imaging and

cancer treatment [1–4]. However, the same properties that enable biological activity may also create unexpected toxicological effects. A central principle emerging by 2012 was therefore that nanoparticles should be treated as complex, dynamic entities rather than as miniature versions of their bulk materials [5,6]. The aim of this review is to synthesize the literature available up to December 2012 concerning the major classes and synthesis routes of biologically relevant nanoparticles, their interactions with living systems, biomedical applications, safety profiles, translational challenges and future opportunities.

2. Classification and Synthesis of Biological Nanoparticles

Nanoparticles used in biology can be classified broadly according to composition. Metallic nanoparticles include gold, silver and related metals. Gold nanoparticles are attractive because their optical response and surface chemistry can be tuned, whereas silver nanoparticles have been widely investigated for antimicrobial activity. Metal-oxide nanoparticles include iron oxides, titanium dioxide, zinc oxide and silica-based structures. Superparamagnetic iron-oxide nanoparticles are especially important for magnetic manipulation, separation, imaging and hyperthermia. Semiconductor quantum dots provide size-dependent fluorescence and have been explored as bright imaging labels, although concerns about heavy-metal constituents have limited some biological uses.

Organic nanocarriers include polymeric nanoparticles, polymeric micelles, dendrimers, liposomes and other lipid-based systems. These platforms can encapsulate poorly soluble molecules, protect unstable drugs or nucleic acids and provide controlled release. Liposomes are particularly important historically because they established the clinical feasibility of nanoscale drug carriers. Hybrid particles combine organic and inorganic components to integrate functions such as imaging, targeting and therapy [2–4].

Synthesis may be physical, chemical or biological. Chemical routes commonly use reduction, precipitation, sol–gel processing, emulsion methods or polymerization, followed by stabilization with surfactants, polymers or ligands. Physical methods include evaporation–condensation, milling and related top-down approaches. These routes can provide good control but may require high energy, organic solvents or reagents that must be removed before biological use.

Biological synthesis became increasingly important as an alternative route. Bacteria, fungi, algae and other biological systems can reduce metal ions and promote nanoparticle formation. Microbial synthesis can occur intracellularly, where ions are transported into cells and transformed by cellular components, or extracellularly, where secreted enzymes and biomolecules participate in reduction and stabilization [7]. Fungi received particular attention because they can produce large quantities of extracellular enzymes and metabolites and can be comparatively convenient for downstream processing [8]. Biological synthesis is attractive because it can operate under relatively mild conditions and may reduce reliance on harsh reagents. Nevertheless, reproducibility, purification, control of size distribution, biological contamination and scale-up remain important limitations.

For biological applications, synthesis cannot be separated from characterization. Size and size distribution should be evaluated by complementary methods such as electron microscopy and dynamic light scattering; surface charge can be estimated by zeta potential; composition and crystallinity can be assessed using spectroscopic and diffraction techniques; and surface coatings require chemical characterization. Measurements should also be repeated in relevant biological media because salts and proteins can substantially change hydrodynamic size and aggregation.

3. Mechanisms of Interaction with Biological Systems

The biological behavior of a nanoparticle begins at the interface between its surface and the surrounding fluid. When nanoparticles enter blood, serum-containing culture medium or other biological fluids, proteins, lipids and other biomolecules adsorb to the surface. By 2012, the concept of the biomolecular or protein corona had become central to understanding nano–bio interactions. The corona can give a particle a biological identity that differs from its initially engineered synthetic identity [9,10]. Its composition depends on particle size, shape, surface chemistry, the biological fluid and exposure time. Corona formation has several consequences. Adsorbed proteins may mask targeting ligands, alter recognition by receptors, influence complement activation, change colloidal stability and modify uptake by phagocytic cells. Thus, a nanoparticle designed to recognize a specific cell in buffer may behave differently in plasma. This observation explains why characterization under physiological conditions is essential and why successful targeting requires more than attaching a ligand to a particle surface. Cellular entry occurs through several mechanisms, including

phagocytosis, macropinocytosis and receptor-mediated or other forms of endocytosis. The dominant route depends on both particle properties and cell type. After internalization, nanoparticles may be transported through endosomes and lysosomes, escape into the cytoplasm, undergo degradation or remain sequestered. Intracellular localization is therefore critical for drug and gene delivery because the therapeutic payload must reach the appropriate compartment.

At the organism level, biodistribution is shaped by size, surface coating, charge, aggregation, protein adsorption and the mononuclear phagocyte system. Nanoparticles may accumulate in liver and spleen, while renal clearance is strongly influenced by effective size and surface characteristics. For tumor delivery, nanoscale carriers were widely investigated for passive accumulation associated with abnormal tumor vasculature, although the magnitude of this effect can vary among models and tumors [3].

Nano-bio interactions can also trigger adverse responses. Reactive oxygen species, membrane damage, mitochondrial dysfunction, inflammatory signaling and DNA damage have been reported for some nanomaterials under particular conditions [5,11]. Importantly, these effects are not universal properties of all nanoparticles. Toxicity depends on composition, dissolution, surface reactivity, impurities, dose, exposure duration and biological context. Therefore, mechanistic interpretation requires well-characterized materials and meaningful dose metrics

4. Biological and Biomedical Applications

Drug delivery is one of the most developed biomedical applications of nanoparticles. Nanocarriers can improve the apparent solubility of hydrophobic compounds, protect drugs from premature degradation, modify pharmacokinetics and release payloads in a controlled manner. Surface modification with polyethylene glycol or other hydrophilic polymers can reduce nonspecific interactions and prolong circulation in some systems. Targeting ligands such as antibodies, peptides, sugars or small molecules can be attached to promote interactions with selected receptors. By 2012, several nanoparticle-based cancer medicines were already in clinical use and additional formulations were under investigation, demonstrating that nanoscale delivery could move beyond laboratory proof-of-concept [3].

Cancer nanomedicine has exploited both passive and active targeting concepts. Passive strategies attempt to use tumor-associated vascular abnormalities, whereas active strategies add ligands that bind cellular or vascular targets. Nanoparticles can also carry combinations of drugs, imaging agents or nucleic acids. Such multifunctional systems encouraged the concept of “theranostics,” in which diagnosis and therapy are integrated in a single platform.

Imaging is another major application. Iron-oxide nanoparticles can alter magnetic resonance contrast and can also be manipulated with magnetic fields. Gold nanoparticles exhibit optical properties useful for sensing and photothermal approaches. Quantum dots offer intense and relatively photostable fluorescence for cellular and molecular imaging, although their long-term fate and composition require careful safety evaluation. Nanoparticles have also been explored as contrast-enhancing agents for multimodal imaging [4].

In biosensing, the high surface area of nanoparticles allows dense immobilization of recognition molecules, while optical, electrical or magnetic properties can transduce binding events. Gold nanoparticles, quantum dots and magnetic particles have been investigated for detection of nucleic acids, proteins, pathogens and other analytes. Magnetic nanoparticles additionally enable rapid separation and concentration of biological targets before detection.

Gene delivery represents another important area. Cationic polymers, lipids and engineered nanoparticles can associate with DNA or RNA, protect nucleic acids from degradation and facilitate cellular entry. The principal challenge is achieving efficient delivery while avoiding toxicity and ensuring release at the correct intracellular location.

Biologically synthesized nanoparticles have also been investigated for antimicrobial activity, biosensing, separation and cancer-related applications [7]. Their potential advantage is the use of biological reducing and capping molecules, but biomedical translation requires precise knowledge of the resulting surface composition and consistent purification.

5. Biocompatibility, Toxicity and Safety Profiles

Biocompatibility is not an intrinsic yes-or-no property of a nanoparticle. It is a relationship among the material, dose, route of administration, duration of exposure and biological system. A formulation that is well tolerated after local administration may behave differently after intravenous or inhalational exposure. Consequently, safety evaluation must consider both acute responses and longer-term distribution, persistence and clearance.

Oxidative stress is among the most frequently discussed mechanisms of nanoparticle toxicity. Some materials can generate reactive oxygen species directly or indirectly, disturbing cellular redox balance. Excessive oxidative stress can damage proteins, lipids and nucleic acids and can activate inflammatory pathways. Dissolution of metal-containing nanoparticles may release ions that contribute to toxicity, while surface contaminants or synthesis residues can confound interpretation. Aggregation also changes effective size and sedimentation, potentially altering the delivered cellular dose. Toxicological studies face methodological challenges. Nanoparticles may interfere with colorimetric or fluorescent assays, making apparent cytotoxicity difficult to interpret without controls. Mass concentration alone may not adequately describe dose when particle number or surface area is biologically relevant. Elsaesser and Howard emphasized the importance of material characterization, dose and exposure pathways for nanotoxicological assessment [5]. Sharifi and colleagues similarly reviewed the need to relate physicochemical characteristics to biological responses and to examine multiple exposure routes [11]. Safety-by-design therefore requires control of composition, surface chemistry, degradability and impurities from the earliest stages of development. In vitro testing should be complemented by appropriate in vivo studies when justified, with attention to pharmacokinetics, organ accumulation, immune responses and excretion. The protein corona should also be considered because it can modify both cellular interactions and immune recognition [9,10].

5.1 Determinants of Biological Performance

A useful way to compare nanoparticle platforms is to consider the relationship between material properties and biological function. Small particles provide high specific surface area and can access biological spaces unavailable to larger carriers, but decreasing size can also increase surface reactivity and alter clearance. Shape influences hydrodynamic behavior and the area of contact with cell membranes. Surface charge affects dispersion and electrostatic interactions: strongly charged particles may bind proteins and membranes efficiently, yet these interactions can also promote nonspecific uptake or toxicity. Neutral or sterically protected surfaces can reduce some nonspecific interactions, although adsorption of biomolecules may still occur after exposure to biological fluids. These relationships show why optimization for a single property, such as maximum cellular uptake, does not necessarily produce the safest or most effective formulation.

Surface functionalization is equally important. Polymeric coatings can improve colloidal stability and provide chemical groups for attachment of drugs, antibodies, peptides or other ligands. Targeting is most effective when ligand density, orientation and accessibility remain suitable after the particle encounters serum proteins. The protein-corona literature available by 2012 suggested that biological fluids can partly obscure an engineered surface and thereby modify receptor recognition [9,10]. For this reason, evaluation of targeting should include experiments in relevant protein-containing media rather than relying exclusively on simplified buffers.

The fate of the carrier and the fate of its payload should also be distinguished. A nanoparticle may remain in a tissue after a drug has been released, or it may degrade into products with different distributions and toxicities. Biodegradable polymers and lipids offer potential advantages because their components can be metabolized or eliminated, whereas persistent inorganic materials require careful study of long-term retention. Conversely, inorganic nanoparticles may provide optical or magnetic functions that organic carriers cannot easily reproduce. Platform selection should therefore be driven by the intended biological task, required duration of function, route of administration and acceptable persistence rather than by a universal ranking of nanoparticle types.

For experimental comparison, a minimum characterization set should include particle composition, primary size and morphology, hydrodynamic size in the exposure medium, size distribution, surface charge, coating or ligand identity, concentration, aggregation state and stability over the experimental period. Drug-delivery systems additionally require measurement of loading, encapsulation efficiency and release kinetics. Toxicology experiments should document the administered and, where possible, delivered dose and should include controls for assay interference. Such reporting strengthens reproducibility and helps distinguish true material-dependent effects from differences caused by preparation or measurement.

The most convincing biomedical designs therefore combine three forms of evidence: physicochemical characterization, mechanistic biological testing and application-specific performance. A particle that produces a strong imaging signal but causes unacceptable inflammation is not a successful imaging agent; similarly, a carrier that shows high drug loading but rapidly aggregates in serum is unlikely to translate effectively. The emerging nanomedicine literature through 2012 increasingly supported this integrated view, linking material engineering to pharmacology, biological identity and safety [3–5,9–12].

6. Current Challenges and Regulatory Hurdles

The principal translational challenge is reproducibility. Nanoparticle products are multi-component systems whose biological behavior can change with relatively small differences in size distribution, morphology, surface coating, residual reagents or aggregation. Manufacturing processes must therefore control critical quality attributes across batches and during scale-up. Desai identified detailed physicochemical analysis, reproducible manufacturing, biological characterization and scale-up as major challenges for nanoparticle therapeutics [12].

A second challenge is the gap between simplified laboratory models and human biology. Cell cultures cannot fully reproduce blood flow, immune clearance, tissue barriers or long-term metabolism. Animal models provide additional information but may not predict human biodistribution or toxicity quantitatively. Standardized reference materials, validated assays and harmonized reporting are needed to make results comparable among laboratories.

Regulatory assessment is complicated because nanoparticle formulations may combine a drug, carrier, targeting ligand and imaging component. The relevant attributes can include particle size, polydispersity, surface chemistry, drug loading, release kinetics, sterility, stability and biological identity. Regulatory decisions therefore require a product-specific, evidence-based approach rather than assuming that all nanomaterials share a common risk profile.

Environmental and occupational exposure also deserve attention. Production, handling and disposal may expose workers or ecosystems to nanomaterials through routes different from those intended for patients. By 2012, significant uncertainty remained concerning chronic exposure, persistence and environmentally relevant dose–response relationships [5,11].

7. Future Perspectives and Conclusion

The literature available through 2012 shows that nanoparticles had already become important tools for biology and medicine, but it also demonstrates that successful application depends on understanding the dynamic nano–bio interface. Future systems were expected to move toward multifunctional and stimuli-responsive designs that combine targeting, controlled release, imaging and therapy. Improved biodegradable materials and better control of surface chemistry could reduce long-term accumulation, while biological synthesis offered a promising route toward milder fabrication methods if reproducibility and purification could be solved.

A particularly important direction is predictive characterization. Rather than evaluating a nanoparticle only in water or buffer, future development should examine how its identity changes in realistic biological fluids and how those changes affect transport, cellular uptake, immune recognition and toxicity. Protein-corona research had already made clear by 2012 that the biological environment can substantially reshape nanoparticle behavior [9,10].

In conclusion, nanoparticles provide a versatile bridge between nanoscale materials and biological systems. Metallic, magnetic, polymeric, lipid and semiconductor nanoparticles support applications ranging from drug delivery and imaging to biosensing, gene delivery and antimicrobial technologies. Their advantages arise from tunable size, surface chemistry and functional properties, but these same features demand rigorous characterization and safety assessment. Translation to reliable biomedical products requires reproducible manufacturing, mechanistic understanding of biological interactions, standardized toxicology and careful evaluation of long-term fate. The central lesson of the pre-2013 literature is that effective nanobiotechnology must integrate material design, biological identity and safety rather than treating them as separate problems.

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11. Ethical Approval

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12. Informed Consent

Informed consent was not applicable because this study did not involve human participants.

13. Institutional Review Board Statement

Institutional Review Board approval was not required because this study is a literature-based review and did not involve human participants or animals.

14. Data Availability Statement

Data availability was not applicable because this article is based on information obtained from previously published literature.

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