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Review Paper

Active Nanotherapeutics: Nanoparticles as Therapeutic Agents in Next-Generation Medicine (2026)

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ABSTRACT

Nanomedicine has rapidly evolved from its initial role as passive drug carriers into active, intelligent, and programmable therapeutic agents. Early nanoparticle systems such as liposomes and polymeric carriers improved solubility, bioavailability, and circulation time, but their function was largely supportive. Recent advances have introduced programmable nanoparticles, autonomous nanotherapeutics, nanorobotics, and AI driven design strategies, enabling site specific delivery, real time adaptability, and multifunctional theranostics. Physically activated nanoparticles including photothermal, magnetic, ultrasound, and photoacoustic systems further expand therapeutic precision by responding to external stimuli. Clinically, nanomedicine has already demonstrated impact in oncology, infectious diseases, and diagnostics, with several formulations approved and many in advanced trials. Future perspectives emphasize personalized nanomedicine, regulatory harmonization, and integration of nano bio interactions with digital health platforms. This transition marks a paradigm shift, positioning nanotherapeutics as dynamic partners in healthcare, bridging diagnostics and therapy, personalization and scalability, and innovation with accessibility

INTRODUCTION

1.1 Evolution of nanomedicine:

The evolution of medicines reflects humanity's constant pursuit of better ways to heal and protect life. In the earliest civilizations, treatment relied on natural remedies plants, minerals, and traditional practices that were passed down through generations. These therapies were empirical, based on observation and cultural wisdom rather than scientific validation. With the rise of chemistry in

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the 18th and 19th centuries, medicine entered a new phase where purified compounds such as morphine and quinine became available, marking the beginning of modern pharmacology (1). The 20th century brought the synthetic revolution, introducing antibiotics, vaccines, and chemically engineered drugs that transformed healthcare by reducing mortality and enabling mass production with standardized quality. As biotechnology advanced, the late 20th and early 21st centuries witnessed the emergence of biologics monoclonal antibodies, recombinant proteins, and gene therapies that offered precision by targeting specific molecular pathways. This era laid the foundation for personalized medicine, where treatments were tailored to individual genetic and biological profiles. Today, medicine is entering the age of nanotherapeutics, where nanoparticles are not merely passive carriers but active therapeutic agents themselves (2). Hafnium oxide nanoparticles enhancing radiotherapy, ultrasmall silica nanoparticles remodeling tumor microenvironments, and gold nanocrystals protecting neurons in neurodegenerative disorders exemplify this paradigm shift. The trajectory from herbal remedies to nanomedicine demonstrates a clear progression toward precision, personalization, and active intervention, underscoring how each era of medicine builds upon the last to meet the evolving challenges of human health.

1.2 From passive drug carriers to active nanotherapeutics:

For decades, nanoparticles were primarily designed as passive drug carriers, serving as vehicles to encapsulate therapeutic molecules and deliver them to specific sites in the body. Liposomes, polymeric nanoparticles, and solid lipid carriers became the backbone of nanomedicine, improving solubility, prolonging circulation time, and enhancing bioavailability of drugs that otherwise faced rapid degradation or poor absorption. Their role was supportive protecting the drug and guiding it to its destination without contributing any intrinsic therapeutic activity of their own (3).

However, the landscape of nanomedicine has shifted dramatically with the emergence of active nanotherapeutics. In this paradigm, nanoparticles themselves act as therapeutic agents, independent of any drug cargo. Hafnium oxide nanoparticles, for instance, amplify radiotherapy by directly interacting with tumor tissues, while ultrasmall silica nanoparticles remodel the tumor microenvironment to suppress cancer progression. Similarly, gold nanocrystals (CNM-Au8) demonstrate neuroprotective effects in neurodegenerative disorders, offering therapeutic benefits without conventional drug loading. This transition from passive to active systems represents a paradigm shift in medicine. Instead of merely serving as inert carriers, nanoparticles are now engineered to interact dynamically with biological pathways modulating immune responses, altering cellular signaling, and even functioning as radiosensitizers or enzyme mimetics (4).

1.3 Definition and significance of active nanoparticles:

Active nanoparticles are a new generation of nanomedicines designed not merely to transport therapeutic agents but to exert intrinsic biological activity themselves. Unlike conventional nanocarriers, which act as passive vehicles, active nanoparticles interact directly with cellular and molecular pathways to produce therapeutic effects. Their activity may arise from physical properties such as radioenhancement by hafnium oxide nanoparticles or chemical and biological interactions, such as ultrasmall silica nanoparticles remodeling the tumor microenvironment or gold

nanocrystals providing neuroprotection in neurodegenerative disorders (5).

The significance of active nanoparticles lies in their ability to redefine the role of nanomedicine. They represent a paradigm shift from drug delivery systems to functional therapeutic agents, capable of addressing limitations of traditional medicines. By combining precision targeting with intrinsic activity, they offer several advantages:

- **Enhanced efficacy:** Direct modulation of disease pathways without relying solely on drug cargo.
- **Reduced dependency on conventional drugs:** Potential to minimize systemic toxicity and drug resistance.
- **Novel mechanisms of action:** Radiosensitization, immune activation, and enzyme-mimetic activity expand therapeutic possibilities.
- **Clinical translation potential:** Early trials in oncology and neurology demonstrate promising outcomes, positioning active nanoparticles as candidates for next-generation therapies.

1.4 Scope of the review:

This review aims to provide a comprehensive exploration of Active Nanotherapeutics: Nanoparticles as Therapeutic Agents in Next-Generation Medicine (2026). The scope extends beyond conventional drug delivery systems to highlight how nanoparticles themselves are emerging as functional therapeutic entities. It will cover the historical transition from passive nanocarriers to active nanoparticles, define their unique mechanisms of action, and emphasize their clinical significance in oncology, neurology, and immunotherapy.

The review will also examine cutting-edge examples such as hafnium oxide nanoparticles used as radioenhancers, ultrasmall silica nanoparticles for tumor microenvironment remodeling, and gold nanocrystals demonstrating neuroprotective effects (6). In addition, it will integrate perspectives on phytopharmaceutical-based nanotherapeutics, where herbal actives like curcumin, berberine, and guggul are being engineered into hybrid nanoparticle systems for enhanced efficacy.

2. Concept and Classification of Active Nanotherapeutics

2.1 Intrinsically active nanoparticles:

Intrinsically active nanoparticles mark a turning point in nanomedicine because they are not just carriers of drugs but therapeutic agents in their own right. Their activity comes from the unique properties of the material itself whether it is the ability to amplify radiation, mimic enzymes, or directly influence cellular signaling. This makes them fundamentally different from traditional nanocarriers, which only serve to protect and deliver drugs. For example, hafnium oxide nanoparticles have shown promise in cancer therapy by intensifying the effects of radiotherapy, allowing tumors to be treated more effectively without increasing damage to healthy tissues. Ultrasmall silica nanoparticles can reshape the tumor microenvironment, making it less supportive of cancer growth, while gold nanocrystals (CNM-Au8) are being studied for their neuroprotective effects in diseases like ALS (7). In addition, certain iron oxide nanoparticles act as “nanozymes,” mimicking natural enzymes to reduce oxidative stress and inflammation. The importance of intrinsically active nanoparticles lies in their ability to open new therapeutic pathways that conventional drugs cannot achieve.

2.2 Stimuli-responsive nanoparticles:

Stimuli-responsive nanoparticles represent one of the most innovative directions in nanomedicine,

designed to respond intelligently to specific biological or external triggers. Unlike conventional systems that release drugs in a continuous or uncontrolled manner, these nanoparticles remain stable until they encounter a defined stimulus such as changes in pH, temperature, redox potential, enzymes, or even external signals like light, ultrasound, or magnetic fields. Once triggered, they undergo structural or chemical changes that lead to controlled drug release or activation of therapeutic functions. The concept is rooted in the idea of precision therapy delivering treatment only when and where it is needed. For example, tumor tissues often exhibit acidic microenvironments, and pH-sensitive nanoparticles can exploit this difference to release anticancer drugs selectively at the tumor site. Similarly, redox-responsive nanoparticles can react to elevated glutathione levels inside cancer cells, ensuring intracellular drug release (8). Enzyme-responsive systems are designed to degrade in the presence of disease-specific enzymes, while externally triggered nanoparticles allow clinicians to control therapy using light or magnetic fields.

The significance of stimuli-responsive nanoparticles lies in their ability to minimize systemic toxicity, enhance therapeutic efficacy, and improve patient compliance. They embody the principle of "smart medicine," where treatment adapts dynamically to the biological environment. Recent advances include hybrid systems that combine multiple stimuli responses, offering even greater precision and adaptability (9).

2.3 Catalytic/nanozyme systems:

Catalytic nanoparticles, often referred to as nanozymes, are an exciting class of intrinsically active nanotherapeutics that mimic the activity of natural enzymes. Unlike conventional enzymes, which are proteins with limited stability and high production costs, nanozymes are engineered nanomaterials that display enzyme-like catalytic functions while offering superior robustness, tunability, and scalability.

The concept of nanozymes emerged from the discovery that certain nanoparticles such as iron oxide, cerium oxide, and gold could catalyze biochemical reactions similar to peroxidases, oxidases, or superoxide dismutases. These catalytic properties allow them to regulate oxidative stress, degrade harmful biomolecules, and modulate cellular signaling pathways. For instance, iron oxide nanozymes have been shown to reduce reactive oxygen species (ROS) in inflamed tissues, while cerium oxide nanoparticles can switch between oxidation states to provide long-lasting antioxidant protection (10).

The significance of catalytic/nanozyme systems lies in their versatility and therapeutic potential. They can be applied in oncology to generate reactive oxygen species for tumor destruction, in neurology to protect neurons from oxidative damage, and in infectious diseases to disrupt bacterial biofilms.

2.4 Physically activated nanoparticles:

Physically activated nanoparticles are a fascinating class of nanotherapeutics that rely on external physical stimuli such as light, heat, ultrasound, or magnetic fields to trigger their therapeutic activity. Unlike chemically or biologically responsive systems, these nanoparticles remain inert until exposed to a controlled physical signal, which then activates their function. This makes them highly versatile, as clinicians can regulate the timing, location, and intensity of therapy with precision (11).

For example, photothermal nanoparticles (such as gold nanorods or carbon-based nanostructures) absorb near-infrared light and convert it into heat, selectively destroying tumor cells while sparing healthy tissue. Magnetic nanoparticles can be guided to specific sites using external magnetic

fields and then activated to produce localized hyperthermia or enhance imaging. Ultrasound-responsive nanoparticles are engineered to release drugs or generate cavitation effects when exposed to focused ultrasound waves, offering non-invasive control over therapy (12). Similarly, photoacoustic nanoparticles combine light absorption with acoustic signal generation, enabling both treatment and real-time monitoring. The significance of physically activated nanoparticles lies in their ability to provide on-demand, site-specific therapy, reducing systemic side effects and improving patient safety.

2.5 Immunomodulatory nanoparticles:

Immunomodulatory nanoparticles are a rapidly emerging class of nanotherapeutics designed to interact directly with the immune system, either by enhancing its activity against disease or by suppressing unwanted immune responses. Unlike conventional drugs that broadly stimulate or inhibit immunity, these nanosystems provide precision control, tailoring immune modulation to the specific needs of the patient (13).

The concept builds on the ability of nanoparticles to deliver immune-regulating molecules or to act as immune modulators themselves. For example, nanoparticles can present antigens in a highly organized manner to boost vaccine efficacy, or they can carry immunosuppressive agents to reduce inflammation in autoimmune disorders. Some nanoparticles, such as logic-gated STING-agonistic systems, are engineered to activate immune pathways only in the presence of disease-specific signals, thereby minimizing off-target effects (14). Others, like polymeric or lipid-based nanocarriers, are used to deliver checkpoint inhibitors or cytokines directly to the tumor microenvironment, enhancing cancer immunotherapy.

The significance of immunomodulatory nanoparticles lies in their versatility: In oncology, they can reprogram the tumor microenvironment, making cancer cells more visible to the immune system. Also in infectious diseases, they can boost vaccine responses by acting as adjuvants.

3. Nanoparticle Platforms

3.1 Lipid nanoparticles:

Lipid nanoparticles (LNPs) are among the most established and versatile platforms in nanomedicine, widely recognized for their biocompatibility and ability to mimic natural biological membranes. Built from lipids arranged in nanoscale structures, they provide a safe and efficient way to encapsulate therapeutic molecules ranging from small drugs to complex biomacromolecules like RNA (15). Their amphiphilic nature allows them to carry both hydrophilic and hydrophobic agents, making them adaptable for diverse therapeutic applications.

Table 1: Key types and their roles.

Type	Structure	Function	Example Application
Liposomes	Bilayer vesicles	Encapsulate hydrophilic & hydrophobic drugs	Doxorubicin liposomes in cancer therapy (16)
Solid Lipid Nanoparticles (SLNs)	Solid lipid core	Stable carriers for poorly soluble drugs	Oral delivery of anti-HIV drugs
Nanostructured Lipid Carriers (NLCs)	Mix of solid + liquid lipids	Higher drug loading, controlled release	Anti-inflammatory gels

RNA-LNPs	Ionizable lipids + helper lipids	Protect fragile RNA, enable intracellular delivery	mRNA vaccines (COVID-19, cancer immunotherapy)(17)

3.2 Polymeric nanoparticles:

Polymeric nanoparticles are like the "engineered scaffolds" of nanomedicine, built from biodegradable polymers such as PLGA, PEG, and chitosan. Their strength lies in the ability to control drug release with precision, making them ideal for therapies that require sustained action over days or weeks (18).

The story of polymeric nanoparticles unfolds across several distinct designs:

- **Polymeric Micelles** – These are formed when amphiphilic polymers self-assemble into tiny spheres. Their hydrophobic core can solubilize poorly water-soluble drugs, while the hydrophilic shell ensures stability in the bloodstream. They are widely used in oncology to deliver anticancer agents that otherwise fail to dissolve.
- **Dendrimers** – Imagine a tree with multiple branches; dendrimers are highly branched polymers that provide numerous attachment points for drugs, genes, or imaging agents. Their multivalency makes them powerful tools for combination therapy, where multiple molecules can be delivered simultaneously.
- **PLGA Nanoparticles** – PLGA (poly lactic-co-glycolic acid) is FDA-approved and one of the most reliable polymers in drug delivery. It degrades into lactic acid and glycolic acid, both naturally metabolized by the body. PLGA nanoparticles are used for controlled release formulations, ensuring steady therapeutic levels without frequent dosing (19).
- **Chitosan Nanoparticles** – Derived from natural sources, chitosan is bioadhesive and particularly effective for mucosal delivery. It has been explored for nasal vaccines, oral drug delivery, and even wound healing applications, thanks to its ability to interact with biological membranes (20).

Together, these designs showcase the diversity and adaptability of polymeric nanoparticles. They can be tuned for solubility, targeting, biodegradability, or responsiveness to stimuli, making them a flexible platform across oncology, infectious diseases, and regenerative medicine.

3.3 Metallic and metal-oxide nanoparticles:

Metallic and metal oxide nanoparticles are a powerful class of nanotherapeutics that derive their activity from the unique physicochemical properties of metals at the nanoscale. Unlike organic carriers, these nanoparticles often possess intrinsic therapeutic functions such as radiosensitization, antimicrobial activity, or catalytic behavior that make them more than just delivery vehicles.

Metallic nanoparticles like gold, silver, and platinum are widely studied for their biomedical applications. Gold nanoparticles, for instance, are used in photothermal therapy, where they absorb near-infrared light and convert it into heat to selectively destroy tumor cells. Silver nanoparticles are valued for their broad-spectrum antimicrobial properties, making them useful in wound healing and infection control. Platinum nanoparticles have shown promise in oncology, acting both as drug carriers and as agents that enhance chemotherapy efficacy (21).

Metal oxide nanoparticles add another dimension to nanomedicine. Hafnium oxide nanoparticles are clinically tested as radioenhancers, amplifying the effects of radiotherapy in cancer treatment. Cerium oxide nanoparticles are known for their redox-switching ability, functioning as long-

lasting antioxidants that protect tissues from oxidative stress. Iron oxide nanoparticles, meanwhile, serve dual roles: they act as nanozymes with enzyme-like activity to regulate reactive oxygen species, and they are also used as contrast agents in magnetic resonance imaging (MRI), bridging therapy and diagnostics. The significance of metallic and metal oxide nanoparticles lies in their multifunctionality. They can simultaneously act as therapeutic agents, diagnostic tools, and delivery systems, embodying the concept of theranostics. Their tunable size, shape, and surface chemistry allow researchers to design nanoparticles that respond to external stimuli (light, magnetic fields) or internal biological cues, making them adaptable to diverse clinical needs (22).

In essence, metallic and metal oxide nanoparticles represent a fusion of physics, chemistry, and medicine, offering smart solutions for cancer, neurodegenerative diseases, infections, and beyond.

3.4 Silica-based nanoparticles:

Silica-based nanoparticles are a unique platform in nanomedicine, valued for their porous structure, tunable size, and high surface area. These properties make them excellent carriers for drugs, biomolecules, and imaging agents. Unlike metallic or polymeric systems, silica nanoparticles offer remarkable stability and versatility, allowing researchers to design them for both therapeutic and diagnostic purposes (23). The most widely studied form is mesoporous silica nanoparticles (MSNs), which contain well-defined pores that can be loaded with drugs and sealed with stimuli-responsive "caps." This enables controlled release in response to pH, enzymes, or redox conditions. Their surface can be easily functionalized with ligands, antibodies, or polymers, making them highly adaptable for targeted delivery.

Silica nanoparticles are also explored in oncology, where ultrasmall silica particles have shown promise in remodeling the tumor microenvironment, improving drug penetration, and even serving as theranostic agents by combining therapy with imaging (24). In addition, their biocompatibility and ability to degrade into non-toxic silicic acid make them safer compared to many inorganic systems.

3.5 Carbon-based and biomimetic nanoparticles:

- **Carbon-Based Nanoparticles:** Carbon-based nanomaterials such as carbon nanotubes, graphene, fullerenes, and carbon dots are celebrated for their exceptional mechanical strength, electrical conductivity, and surface tunability. Their nanoscale architecture allows them to act as carriers, sensors, or even therapeutic agents. For instance, carbon nanotubes can penetrate cell membranes and deliver drugs directly into cells, while graphene oxide sheets can be functionalized for photothermal therapy in cancer. Carbon dots, with their intrinsic fluorescence, are particularly useful in bioimaging and theranostics, combining visualization with therapy. Importantly, their high surface area enables efficient drug loading and functionalization with targeting ligands, making them adaptable across oncology, neurology, and infectious disease applications (25).
- **Biomimetic Nanoparticles:** Biomimetic nanoparticles take inspiration directly from nature, designed to imitate biological structures or functions. They often use natural components such as cell membranes, proteins, or exosomes to cloak synthetic nanoparticles, thereby enhancing biocompatibility and immune evasion. For example, red blood cell

membrane-coated nanoparticles can circulate longer in the bloodstream, while cancer cell membrane-coated systems can achieve homotypic targeting, delivering drugs specifically to tumor tissues. Exosome-based nanoparticles, derived from natural vesicles secreted by cells, are being explored for regenerative medicine and targeted delivery of genetic material (26).

The significance of these two platforms lies in their complementary strengths. Carbon-based nanoparticles provide robustness, multifunctionality, and advanced physicochemical properties, while biomimetic nanoparticles offer natural camouflage, biological recognition, and improved safety (27). Together, they represent a fusion of engineering and biology, pushing nanomedicine toward therapies that are not only effective but also seamlessly integrated with the body's own systems .

4. Mechanisms of Therapeutic Action

Nanoparticles exert their therapeutic effects through multiple interconnected pathways, including reactive oxygen and nitrogen species (ROS/RNS) generation, induction of oxidative stress, activation of programmed cell death (apoptosis and ferroptosis), organelle-specific targeting (mitochondrial and lysosomal), modulation of immune responses, and enzyme-like catalytic activity (28). Together, these mechanisms contribute to enhanced cellular regulation, selective cytotoxicity, and improved therapeutic efficacy in nanomedicine.

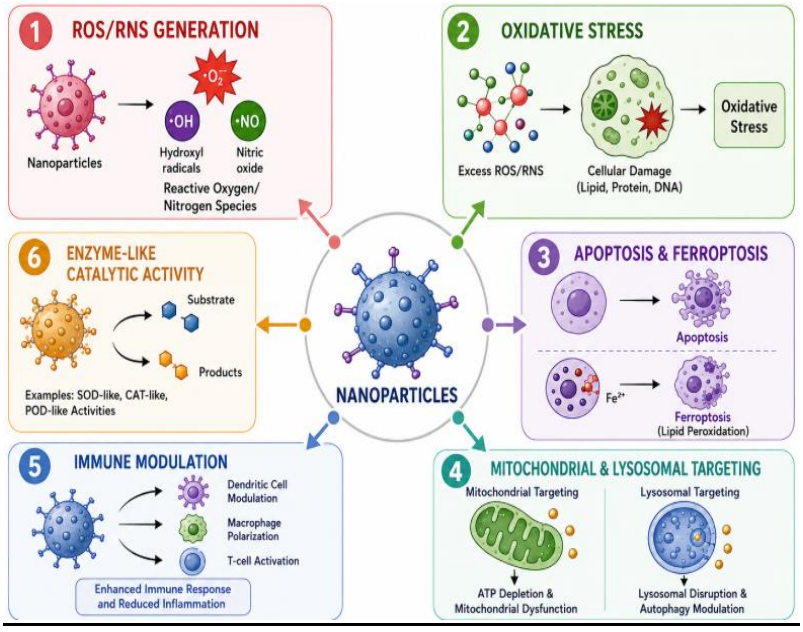

Figure 1: Therapeutic Pathways Mediated by Nanoparticles.

5. Major Therapeutic Applications

Nanoparticles have moved beyond being just experimental carriers they are now central to modern therapeutic strategies across diverse medical fields. Their ability to combine targeted delivery, controlled release, and multifunctionality makes them indispensable in next-generation medicine.

Table 2: Lists specific role of nanotherapeutics in each area.

Application Area	Role of Nanotherapeutics	Examples / Notes
Oncology (Cancer Therapy)	Act as targeted carriers, radiosensitizers, and active therapeutic agents	Gold NPs (photothermal therapy), Hafnium oxide (radioenhancer), RNA-LNPs (immunotherapy) (29).
Infectious Diseases	Provide antimicrobial activity, vaccine delivery, and immune modulation	Silver NPs (antimicrobial), RNA-LNPs (COVID-19 vaccines), polymeric NPs for antiviral drugs (30).
Neurological Disorders	Cross blood–brain barrier, reduce oxidative stress, deliver neuroprotective agents	Cerium oxide NPs (antioxidant), polymeric micelles for Alzheimer's therapy (31).
Cardiovascular & Metabolic Diseases	Enable controlled release, vascular repair, and metabolic regulation	PLGA NPs (anti-hypertensives), lipid NPs (cholesterol regulation) (32).
Regenerative Medicine	Support tissue repair, stem cell growth, and biomimetic delivery	Exosome-based NPs, silica scaffolds for tissue engineering (33).
Theranostics (Therapy + Diagnostics)	Combine imaging and therapy in one platform	Iron oxide NPs (MRI + therapy), carbon dots (bioimaging + drug delivery) (34).

6. Precision and Personalized Nanomedicine

6.1 Targeted nanoparticles:

Targeted nanoparticles are designed to home in on specific cells, tissues, or molecular markers, ensuring that therapeutic agents act precisely where they are needed while minimizing off-target effects. This is the essence of precision nanomedicine making treatment smarter, safer, and more effective (35).

Key Strategies in Targeted Nanoparticles:

- **Ligand-Based Targeting:** Nanoparticles functionalized with antibodies, peptides, or aptamers that bind to disease-specific receptors (e.g., folate receptor in cancer).
- **Stimuli-Responsive Targeting:** Nanocarriers that release drugs only under certain conditions such as acidic pH, high ROS levels, or enzyme activity in diseased tissue.
- **Magnetic/Physical Targeting:** Iron oxide nanoparticles guided by external magnetic fields; gold nanoparticles activated by light for photothermal therapy.
- **Biomimetic Targeting:** Cloaking nanoparticles with cell membranes (e.g., cancer cell membranes, red blood cells) to achieve immune evasion and homotypic targeting.
- **Dual/Multimodal Targeting:** Combining biological ligands with physical stimuli for enhanced specificity (e.g., antibody-functionalized nanoparticles activated by NIR light).

6.2 Biomarker-guided therapy:

Biomarker therapy in nanomedicine focuses on tailoring treatment to the unique molecular signatures expressed by diseased cells, such as proteins, receptors, or genetic mutations. Nanoparticles can be functionalized with ligands, antibodies, or aptamers that specifically recognize these biomarkers, allowing drugs to be delivered with remarkable precision.

For example, HER2-targeted nanoparticles are used in breast cancer to selectively bind tumor cells, while EGFR-directed lipid nanoparticles deliver siRNA in lung cancer. Similarly, PSA-responsive nanocarriers release drugs only in

prostate cancer environments, and exosome-based nanoparticles can carry miRNA tailored to biomarker expression in neurodegenerative diseases (36).

This approach not only enhances therapeutic efficacy but also reduces systemic toxicity by sparing healthy tissues. By integrating biomarker recognition with nanoparticle engineering, biomarker-guided nanotherapy represents a powerful step toward truly personalized medicine, where treatment is designed around the patient's individual biological profile (37).

6.3 AI-assisted nanoparticle design:

Artificial intelligence (AI) is revolutionizing how nanoparticles are conceived, optimized, and translated into therapeutic applications. Instead of relying solely on trial-and-error experiments, AI enables **data-driven design**, where algorithms learn from large datasets of physicochemical properties, biological interactions, and clinical outcomes to propose optimal nanoparticle formulations (38).

Key Roles of AI in Nanoparticle Design (39)**:**

- **Predictive Modeling:** Machine learning predicts how size, shape, charge, and surface chemistry affect biodistribution, toxicity, and therapeutic efficacy.
- **Optimization Algorithms:** AI integrates response surface methodology (RSM) with deep learning to fine-tune formulations for maximum drug loading and controlled release.
- **Virtual Screening:** Computational tools identify the best ligands, polymers, or lipid compositions for targeted delivery.
- **Personalization:** AI links patient biomarker data with nanoparticle design, enabling precision nanomedicine tailored to individual profiles.
- **Automation:** Robotics combined with AI accelerate synthesis and characterization, reducing time and cost.

6.4 Patient-specific nanotherapeutics:

Patient-specific nanotherapeutics are designed to match the unique biological profile of each individual, making treatment highly personalized and precise. The process begins with patient profiling, where genomic, proteomic, and metabolomic data are analyzed to identify disease-specific biomarkers such as mutated genes, abnormal proteins, or receptor overexpression (40).

Based on this information, nanoparticles are engineered with tailored surface modifications antibodies, ligands, or aptamers that can selectively recognize and bind to these biomarkers. Once administered, the nanoparticles achieve targeted delivery, ensuring that therapeutic agents reach only the diseased cells. Controlled release mechanisms, often triggered by pathological conditions like acidic pH, enzyme activity, or oxidative stress, further refine the therapy by activating drugs only in the affected microenvironment (41).

This culminates in a personalized therapeutic effect, which may involve gene silencing, immune modulation, or induction of apoptosis depending on the patient's needs.

7. Safety, Pharmacokinetics and Nano–Bio Interactions

Nanotherapeutics must balance efficacy with safety, and this requires a deep understanding of how nanoparticles behave inside the body. Their small size and unique surface properties allow them to cross biological barriers, but they also raise concerns about toxicity, clearance, and long-term effects (42).

The safety, pharmacokinetics, and nano–bio interactions of nanoparticles are dictated by their design parameters. By adjusting size, surface chemistry, and functionalization, we can predict and control how they move, interact, and clear from the body.

Table 3: Safety considerations, pharmacokinetics, and nano–bio interactions of nanotherapeutics, highlighting how physicochemical properties influence biocompatibility, biodistribution, and therapeutic outcomes.

Aspect	Key Points	Examples / Notes
Safety	Risk of oxidative stress, inflammation, immune activation; surface charge and coating influence cytotoxicity; long-term accumulation in organs	Positively charged NPs → higher hemolysis; PEGylated NPs → improved biocompatibility
Pharmacokinetics (ADME)	**Absorption:** via oral, inhalation, parenteral routes; **Distribution:** depends on size, shape, surface chemistry; **Metabolism:** enzymatic degradation, opsonization; **Excretion:** renal (small NPs), hepatobiliary (large NPs)	PEGylated liposomes → prolonged circulation; <10 nm NPs → renal clearance
Nano–Bio Interactions	Protein corona formation alters identity; cellular uptake via endocytosis; immune response (activation or stealth); barrier crossing (BBB, tumor microenvironment)	Iron oxide NPs → MRI + immune modulation; RBC-coated NPs → immune evasion

8. Clinical Translation and Regulatory Challenges

8.1 Manufacturing and scalability:

Manufacturing and scalability are critical challenges in translating nanotherapeutics from laboratory research to clinical practice. In theory, nanoparticles synthesized in small batches under controlled lab conditions often show excellent reproducibility and performance. However, when production is scaled up to industrial levels, maintaining uniformity in size, shape, surface chemistry, and drug loading becomes difficult. Even minor variations can alter pharmacokinetics, biodistribution, and therapeutic outcomes (43). Scalability also requires standardized protocols and robust quality control systems. Techniques such as microfluidics, high-pressure homogenization, and automated robotic synthesis are being explored to achieve consistent large-scale production. Yet, the cost of specialized equipment and the complexity of multi-component formulations (drug, carrier, targeting ligand, stabilizer) pose significant barriers.

From a regulatory perspective, scalable manufacturing must comply with Good Manufacturing Practices (GMP), ensuring reproducibility, sterility, and safety across batches. This adds another layer of complexity, as nanoparticles are hybrid systems that do not fit neatly into conventional pharmaceutical categories (44).

8.2 Quality control:

Quality control is a cornerstone of nanomedicine manufacturing, ensuring that nanoparticles produced at laboratory or industrial scale remain safe, reproducible, and effective. Theoretically, quality control focuses on monitoring critical parameters such as particle size distribution, surface charge, drug loading efficiency, and release kinetics.

To achieve consistency, standardized analytical techniques are employed — dynamic light

scattering (DLS) for size, zeta potential analysis for surface charge, HPLC/UV spectroscopy for drug content, and electron microscopy for morphology. Stability studies under different storage conditions are also essential to confirm long-term reliability (45).

8.3 Preclinical-to-clinical translation:

The journey of nanotherapeutics from preclinical research to clinical application is complex and requires careful validation at every stage.

Table 4: Preclinical to clinical translation of nanotherapeutics — stages, focus, challenges, and implications.

Stage	Focus	Key Challenges	Example/Implication
Preclinical (in vitro & animal models)	Safety, pharmacokinetics, biodistribution, therapeutic efficacy	Predicting human relevance; protein corona effects; immune responses	Nanoparticles showing tumor targeting in mice may behave differently in humans (46).
Manufacturing (GMP scale-up)	Reproducibility, sterility, batch consistency	Maintaining uniform size, drug loading, surface chemistry at industrial scale	Microfluidic synthesis ensures reproducibility but costly at large scale
Regulatory Approval	Toxicity, long-term safety, nano–bio interactions	Lack of standardized testing protocols; hybrid classification issues	FDA requires detailed ADME and immunogenicity data before human trials
Clinical Trials	Human safety, efficacy, patient variability	Stratified trial designs; biomarker-based grouping; ethical concerns	HER2-targeted nanoparticles tested only in HER2+ breast cancer patients (47).
Translation to Practice	Accessibility, cost, equity	Personalized nanomedicine may be expensive; need for AI-assisted cost reduction	Patient-specific formulations raise affordability and distribution challenges (48).

8.4 Regulatory considerations:

Regulatory considerations in nanomedicine revolve around safety, reproducibility, and classification. Without standardized protocols, approval becomes complex, but compliance with GMP and robust data on nano–bio interactions are essential for clinical acceptance.

Table 5: Key regulatory considerations for nanotherapeutics — requirements, challenges, and implications.

Regulatory Aspect	Requirement	Challenge	Example/Implication
Safety & Toxicity	Detailed data on short-term and long-term effects	Lack of standardized toxicity protocols	Nanoparticles may accumulate in liver/spleen, requiring extended monitoring (49).
Pharmacokinetics & Biodistribution	Comprehensive ADME studies	Variability across nanoparticle types	PEGylated liposomes show prolonged circulation but differ from polymeric NPs
Manufacturing (GMP)	Reproducibility, sterility, validated methods	Complex multi-component formulations	GMP compliance for liposomal drugs like Doxil®

Classification	Clear regulatory category (drug, biologic, device)	Hybrid nature complicates approval	Nanoparticle vaccines blur drug/biologic boundaries
Ethical & Economic	Accessibility, affordability, equity	High cost of patient-specific nanomedicine	Personalized formulations may limit widespread adoption (50).

8.5 Current clinical applications:

Nanomedicine has already begun to reshape clinical practice, with several nanoparticle-based formulations approved and many more in advanced trials. The most notable implication is in **Oncology**, where liposomal drugs (e.g., *Doxil*®) and albumin-bound nanoparticles (*Abraxane*®) (51) have improved drug delivery, reduced toxicity, and enhanced patient outcomes. In **Infectious diseases**, lipid nanoparticles (LNPs) have revolutionized vaccine delivery, as seen in mRNA COVID-19 vaccines, proving their scalability and safety in millions of patients (52).

Another clinical implication lies in **Targeted therapy**. Nanoparticles functionalized with ligands or antibodies enable site-specific delivery, minimizing systemic side effects. This is particularly impactful in cancers, neurological disorders, and cardiovascular diseases. **Diagnostics and imaging** also benefit, with iron oxide nanoparticles used in MRI contrast enhancement and gold nanoparticles explored for biosensing (53).

The broader implication is that nanotherapeutics are moving from being "experimental" to mainstream clinical tools.

FUTURE PERSPECTIVES

The next generation of nanomedicine is envisioned as programmable nanoparticles smart carriers that can be "coded" to respond to specific biological signals, releasing drugs only when and where they are needed. Building on this, autonomous nanotherapeutics will act almost like self-driven systems, capable of sensing disease environments and adapting their behavior without external intervention (54). A particularly futuristic direction is nanorobotics, where nanoscale machines could navigate through the bloodstream, repair tissues, or deliver drugs with surgical precision. Coupled with AI-driven design, these innovations will be optimized using predictive algorithms, ensuring that every nanoparticle is tailored to patient-specific biomarker profiles (55). Finally, the integration of combination therapy and theranostics where nanoparticles simultaneously diagnose and treat disease will transform healthcare into a more personalized, efficient, and preventive system. This convergence of smart design, automation, and multifunctionality points toward a future where nanomedicine is not just a treatment option, but a dynamic partner in maintaining health (56).

CONCLUSION

Nanomedicine has undergone a remarkable transition from its early role as passive drug carriers designed merely to protect and deliver therapeutic molecules, to becoming active, intelligent, and potentially programmable therapeutic agents. Initially, liposomes, polymeric nanoparticles, and solid lipid carriers improved solubility, bioavailability, and circulation time, but their function was supportive rather than therapeutic. Nanoparticles themselves can act as active agents, interacting directly with biological pathways, amplifying radiotherapy, mimicking enzymes, or remodeling disease microenvironments (57).

With advances in programmable nanoparticles, autonomous nanotherapeutics, nanorobotics,

AI-driven design, and theranostic platforms, the field is moving toward systems that are not only carriers but decision-makers capable of sensing, adapting, and responding in real time.

This evolution signifies more than technological progress; it represents a new philosophy of medicine. Nanoparticles are no longer passive tools but dynamic partners in therapy, bridging diagnostics and treatment, personalization and scalability, innovation and accessibility.

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