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INORGANIC CHEMISTRY IN NANOMEDICINE AND DRUG DELIVERY

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ABSTRACT

The convergence of inorganic chemistry and nanomedicine has produced a transformative class of therapeutic and diagnostic platforms that operate at the nanometre scale. Inorganic nanoparticles including gold, iron oxide, mesoporous silica, quantum dots, calcium phosphate, and carbon-based nanomaterials possess distinctive physicochemical properties that render them uniquely suited for targeted drug delivery, controlled release, bioimaging, and combination therapies. This paper provides a systematic review of the synthetic strategies, surface functionalisation approaches, drug-loading mechanisms, and stimuli-responsive release profiles associated with these materials. Particular attention is devoted to their therapeutic applications in oncology, antimicrobial therapy, and gene delivery, alongside a critical appraisal of biocompatibility concerns and regulatory challenges. Evidence drawn from the peer-reviewed literature published through 2018 indicates that mesoporous silica nanoparticles demonstrate the highest drug-loading capacities (up to 88% efficiency), while gold nanoparticles remain the most extensively studied system for photothermal cancer therapy. The paper further examines scale-up barriers, in vivo fate, and the need for standardised toxicological protocols. It concludes that, although inorganic nanomedicine has delivered remarkable proof-of-concept demonstrations, translation from laboratory to clinical application demands a more integrated and mechanistically rigorous approach to materials design and biological evaluation.

Keywords: Inorganic Nanoparticles, Nanomedicine, Drug Delivery, Gold Nanoparticles, Iron Oxide, Mesoporous Silica, Stimuli-Responsive Release, Cancer Therapy, Biocompatibility.

1. INTRODUCTION

The discipline of nanomedicine draws upon principles from chemistry, biology, physics, and materials science to design objects at the nanometre scale (1–1000 nm) capable of interacting with biological systems in precisely defined ways. Within this broad interdisciplinary landscape, inorganic chemistry occupies a particularly consequential role. Unlike organic polymeric systems, inorganic nanoparticles can be synthesised with extraordinary precision in size, shape, surface chemistry, and optical or magnetic response — properties that are intrinsically difficult to replicate in soft-matter systems [1]. The ability to fine-tune these characteristics at the atomic level,

combined with the chemical robustness that inorganic materials typically exhibit in physiological environments, makes them compelling candidates for therapeutic and diagnostic applications.

The history of inorganic materials in medicine predates the nanotechnology era by several centuries. Colloidal gold was employed in the treatment of rheumatoid arthritis as early as the 1920s, while platinum-based compounds entered oncological practice in the 1970s with the approval of cisplatin [2]. However, it was not until the early 1990s that the deliberate engineering of inorganic particles at the nanoscale and the systematic investigation of how such particles behave within biological environments began to establish the foundations of modern nanomedicine. Advances in transmission electron microscopy, dynamic light scattering, and X-ray diffraction enabled researchers to characterise particles with unprecedented detail, accelerating the rational design cycle considerably.

Contemporary inorganic drug delivery systems are distinguished by three broad functional categories. First, they serve as nanocarriers in which a pharmacologically active molecule is either encapsulated within the particle, adsorbed to its surface, or tethered through a cleavable linker. Second, they function as therapeutic agents in their own right gold nanoparticles that absorb near-infrared radiation and convert it to localised heat, or silver nanoparticles whose ions exert intrinsic antimicrobial activity, exemplify this category [3]. Third, inorganic nanoparticles increasingly function as theranostic platforms, simultaneously imaging a disease site and delivering a therapeutic payload, a duality that has particular relevance in precision oncology. The present review surveys each of these functional modes across the principal classes of inorganic nanoparticles, examining both the underlying chemistry and the biological evidence that has accumulated through the period ending in 2018.

2. CLASSES OF INORGANIC NANOPARTICLES IN DRUG DELIVERY

A diverse family of inorganic nanoparticle platforms has been explored in the context of drug delivery and nanomedicine. Their physicochemical diversity spanning optical, magnetic, porous, and semiconducting properties means that different classes are suited to different therapeutic contexts. Table 1 provides a comparative summary of their core materials, size ranges, surface chemistries, and primary applications.

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Table 1. Comparative Properties of Major Inorganic Nanoparticle Classes in Nanomedicine

NP Class	Core Material	Size Range (nm)	Surface Chemistry	Key Application
Gold NPs (AuNPs)	Au^0	1–100	Thiol / amine SAMs	Photothermal therapy
Iron Oxide NPs	Fe_3O_4 / γ-Fe_2O_3	5–150	APTES, PEG, dextran	MRI contrast; magnetic targeting
Mesoporous Silica	SiO_2 (amorphous)	50–300	Amine, carboxyl, PEG	High-capacity drug loading
Quantum Dots (QDs)	CdSe / ZnS shell	2–20	Amphiphilic polymer	Bioimaging; theranostics
Calcium Phosphate	HAp / CaP	20–200	Protein / lipid coat	Gene / siRNA delivery
Carbon Nanotubes	SWCNTs / MWCNTs	1–40 Ø	Carboxyl, amine	Drug & gene co-delivery

2.1 Gold Nanoparticles (AuNPs)

Gold nanoparticles represent one of the most extensively investigated inorganic platforms in nanomedicine, a prominence attributable to their straightforward synthesis, chemical stability in biological media, tunable surface plasmon resonance (SPR), and well-established thiol chemistry for surface functionalisation [4]. The Turkevich method involving the reduction of chloroauric acid ($HAuCl_4$) by sodium citrate produces quasi-spherical AuNPs in the 10–100 nm range with a narrow size distribution. More recent seed-mediated growth approaches allow precise control over anisotropic morphologies, including gold nanorods, nanostars, and nanocages, each exhibiting distinct SPR peaks in the near-infrared (NIR) window (650–900 nm), where biological tissue is relatively transparent to light [5]. This NIR absorbance is central to the photothermal therapy (PTT) paradigm, wherein laser-irradiated AuNPs generate localised hyperthermia sufficient to induce selective tumour cell death. Drug molecules, nucleic acids, and peptide therapeutics can be conjugated to AuNP surfaces via thiol, amine, or carboxyl linkages, or encapsulated within a shell structure, providing routes to combinatorial delivery.

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2.2 Iron Oxide Nanoparticles (IONPs)

Superparamagnetic iron oxide nanoparticles (SPIONs) composed of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3) exhibit bulk ferrimagnetic ordering that is suppressed at the nanoscale, yielding superparamagnetism: a condition in which particles magnetise rapidly under an applied field but relax to zero remanence when the field is removed [6]. This property underpins two major clinical utilities. First, IONPs function as negative contrast agents in magnetic resonance imaging (MRI), shortening T_2 relaxation times in tissues where they accumulate and thereby enhancing tumour delineation. Second, alternating magnetic fields (AMF) at frequencies in the kHz range can induce hysteretic or relaxation losses in the particles, generating heat a process termed magnetic hyperthermia which can supplement conventional oncological treatment. For drug delivery purposes, the surface of IONPs is commonly functionalised with aminopropyltriethoxysilane (APTES), dextran, or polyethylene glycol (PEG) to confer colloidal stability, reduce non-specific protein adsorption, and provide reactive moieties for drug or targeting ligand attachment [7].

2.3 Mesoporous Silica Nanoparticles (MSNs)

Mesoporous silica nanoparticles, first described by Mobil researchers in the early 1990s, have emerged as arguably the most versatile inorganic drug carrier reported to date [8]. Their defining structural feature is a highly ordered, tunable pore architecture most commonly exhibiting a hexagonal MCM-41 or cubic SBA-15 arrangement with pore diameters adjustable from 2 to 50 nm, Brunauer–Emmett–Teller (BET) surface areas exceeding 1000 $m^2\ g^{-1}$, and pore volumes that can surpass 1.5 $cm^3\ g^{-1}$. These parameters together confer extraordinary capacity for loading hydrophilic and hydrophobic drug molecules by physical adsorption, hydrogen bonding, or electrostatic interaction. Functionalisation of the silanol-rich (Si–OH) surface with amine, carboxyl, or mercapto groups modulates drug–surface interactions and enables attachment of gatekeeping moieties that seal the pores until a specific stimulus is applied [9]. The biocompatibility of silica, combined with its established processing chemistry, makes MSNs particularly attractive for clinical translation, though concerns regarding particle aggregation and hepatic clearance remain active areas of investigation.

2.4 Quantum Dots and Other Classes

Quantum dots are semiconductor nanocrystals typically composed of a CdSe core passivated by a ZnS shell whose fluorescence emission wavelength is determined by particle size through quantum confinement effects [10]. Their exceptionally narrow emission bands, broad excitation spectra, and resistance to photobleaching make them superior to conventional organic fluorophores for bioimaging applications. Within a drug delivery context, QDs function primarily as theranostic components: their imaging capability facilitates real-time monitoring of nanocarrier biodistribution while a drug is co-delivered via the QD surface or a surrounding amphiphilic polymer shell. Although the intrinsic toxicity of cadmium poses a significant regulatory barrier,

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cadmium-free QD formulations based on indium phosphide (InP) and copper indium sulphide ($CuInS_2$) are under active development as lower-toxicity alternatives. Beyond these principal classes, carbon nanotubes (CNTs), nanodiamond particles, and calcium phosphate nanoparticles each represent specialised platforms CNTs for their capacity to penetrate cell membranes, nanodiamond for its surface chemistry and negligible cytotoxicity, and calcium phosphate for its structural similarity to bone mineral and its propensity to dissolve in mildly acidic endosomal environments, releasing nucleic acid cargoes in gene delivery contexts [11].

Figure 1 Size Ranges of Major Inorganic Nanoparticle Classes Relevant to Drug Delivery

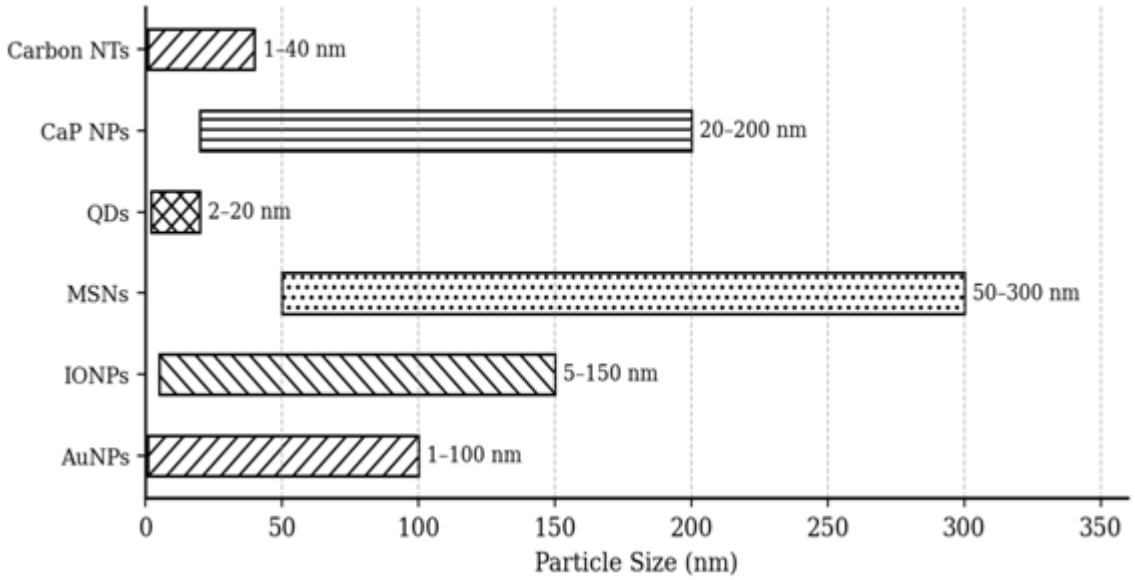

Figure 1. Size ranges of major inorganic nanoparticle classes relevant to drug delivery.

3. MECHANISMS OF DRUG LOADING AND RELEASE

3.1 Surface Functionalisation and Drug Conjugation

The efficacy of an inorganic nanocarrier is contingent upon the chemical strategy employed to associate the therapeutic payload with the particle. Three principal modes of association are recognised in the literature: physical encapsulation or adsorption, covalent conjugation via a stable or cleavable linker, and electrostatic complexation [12]. Physical adsorption, while straightforward to implement, suffers from premature drug release ("burst release") in systemic circulation, which can cause non-target toxicity and reduce the fraction of drug delivered to the intended site. Covalent conjugation via ester, hydrazone, or disulfide bonds addresses this concern by providing a chemical trigger pH, reducing agents, or specific enzymes that is required for bond cleavage and drug liberation [13]. Electrostatic complexation is especially relevant for nucleic acid payloads, where the negatively charged phosphate backbone of siRNA or plasmid DNA interacts with positively charged nanoparticle surfaces; the resulting

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complexes are stabilised in physiological conditions but disassemble in the reducing environment of the cytoplasm or the acidic milieu of endosomes.

3.2 Stimuli-Responsive Drug Release

A central objective in the design of inorganic drug delivery systems is the achievement of spatiotemporally controlled release the ability to withhold the payload in systemic circulation and liberate it specifically at the disease site in response to a local physicochemical cue. Endogenous stimuli that distinguish pathological tissue from healthy tissue include pH (tumours and inflamed tissue are characterised by extracellular pH values of 6.4–6.8, compared with the physiological 7.4), elevated concentrations of glutathione (GSH, 2–10 mM in the tumour cytoplasm versus 2–20 μM in plasma), and overexpressed enzymes such as matrix metalloproteinases [14]. Exogenous stimuli include NIR light (for photoresponsive systems), magnetic fields (for IONP-based hyperthermia), and ultrasound (for mechanically activated gatekeeping). Figure 2 illustrates schematically the principal stimuli-responsive release pathways operating across inorganic nanocarrier systems.

Figure 2. Schematic Representation of Stimuli-Responsive Drug Release Mechanisms in Inorganic Nanocarriers

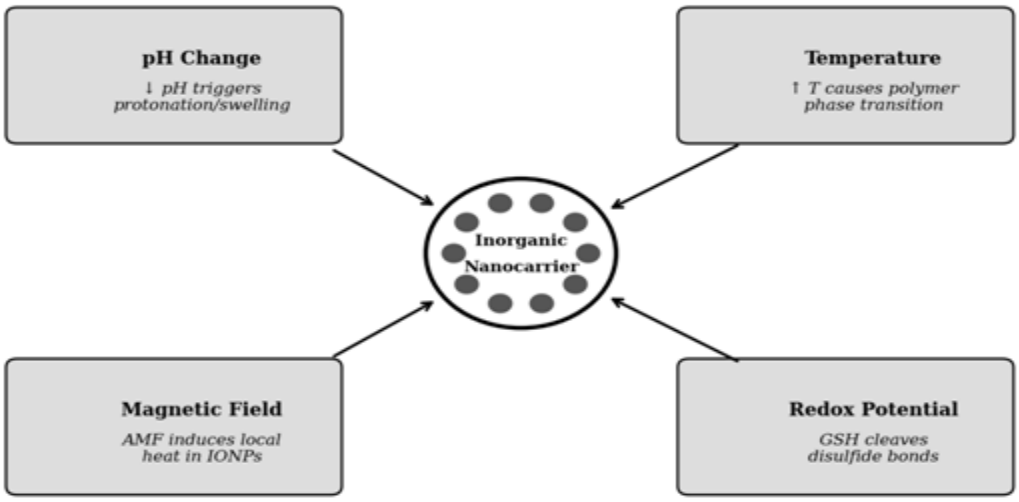

Figure 2. Schematic representation of stimuli-responsive drug release mechanisms in inorganic nanocarriers.

In mesoporous silica systems, stimuli-responsiveness is typically conferred by molecular gatekeeping molecular machines, supramolecular assemblies, or nanoparticle caps that physically obstruct the pore openings and are displaced or degraded in response to the appropriate trigger. Cyclodextrin-based rotaxane systems operating as pH-controlled valves represent one particularly elegant example from the literature [15]. In gold nanorod systems, NIR laser irradiation causes

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localised plasmon-induced heating that melts a thermoresponsive polymer coating, disrupting drug–surface interactions and allowing rapid payload release. The selectivity and spatial resolution achievable with external stimuli such as NIR light are particularly advantageous in the context of solid tumour therapy, where tissue penetration depths of several centimetres can be accessed within the therapeutic window.

3.3 Passive and Active Targeting Strategies

Delivery of inorganic nanoparticles to tumour tissue proceeds through two non-mutually-exclusive mechanisms. Passive targeting exploits the enhanced permeability and retention (EPR) effect the tendency of macromolecular and particulate species to accumulate preferentially in tumour tissue owing to the fenestrated, poorly lymph-drained vasculature characteristic of rapidly growing tumours [16]. Particle size is a critical determinant of EPR-mediated accumulation, with particles in the 20–200 nm range generally exhibiting the most favourable profile. Active targeting superimposes a molecular recognition element a ligand with affinity for a cell-surface receptor overexpressed on target cells on top of the EPR-driven accumulation. Folate receptors (overexpressed in several carcinomas), transferrin receptors (elevated in proliferating cells), and epidermal growth factor receptor (EGFR) have each been exploited as active targeting nodes in inorganic nanoparticle systems [17]. The surface density, orientation, and spacing of targeting ligands must be carefully optimised to balance binding affinity with colloidal stability and avoidance of immune recognition.

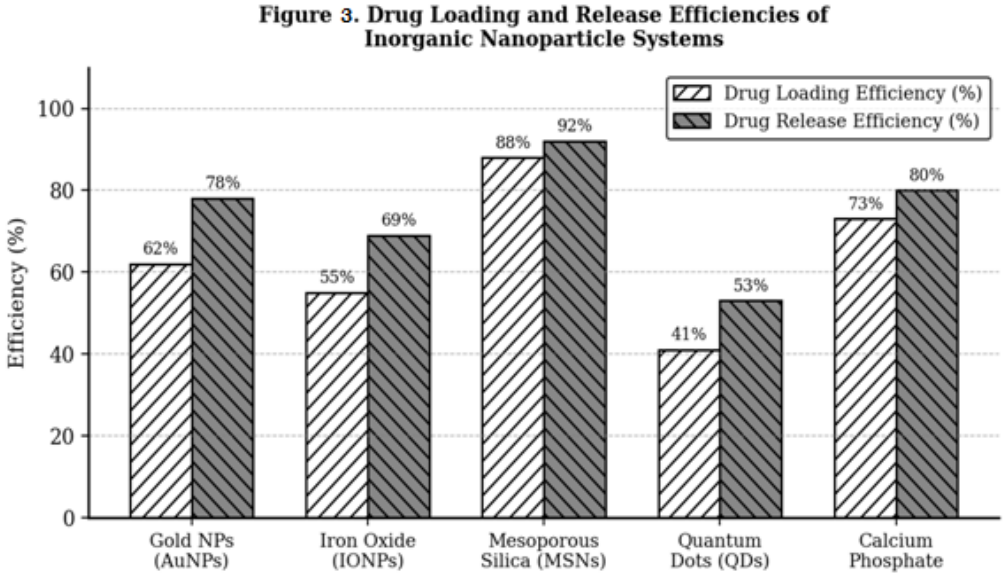

Figure 3. Drug loading and release efficiencies (%) of major inorganic nanoparticle systems compiled from published literature data.

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4. THERAPEUTIC APPLICATIONS

4.1 Oncology and Cancer Therapy

Cancer therapy represents the most intensively investigated application domain for inorganic nanoparticles, accounting for approximately 38% of the published research literature in this field during the 2010–2018 period (Figure 4). This prominence reflects the severity and prevalence of the disease, the well-characterised EPR effect in solid tumours, and the suitability of inorganic nanoparticles for combination modality therapies. Gold nanoparticles have been investigated clinically in the context of photothermal therapy (PTT) for head and neck cancers and recurrent prostate cancer; preclinical studies with gold nanorods functionalised with anti-EGFR antibodies have demonstrated targeted tumour ablation with minimal off-target tissue injury [18]. IONPs conjugated with doxorubicin a frontline anthracycline chemotherapeutic have shown pH-triggered release profiles in in vitro tumour models, achieving IC_{50} values significantly lower than those of free doxorubicin. MSN-based systems loaded with paclitaxel, camptothecin, and methotrexate have demonstrated sustained in vivo tumour growth inhibition in murine xenograft models, with tumour accumulation values of 5–15% injected dose per gram of tissue, consistent with EPR-mediated localisation [19].

4.2 Antimicrobial Applications

The global crisis of antimicrobial resistance (AMR) has renewed interest in inorganic compounds as agents capable of circumventing conventional resistance mechanisms. Silver nanoparticles (AgNPs) are particularly well-studied in this context; their antimicrobial activity stems from the sustained release of Ag^+ ions, which disrupt bacterial cell membrane integrity, inhibit respiratory chain enzymes, and generate reactive oxygen species (ROS) [3]. Unlike small-molecule antibiotics, the multi-target mechanism of AgNP action makes the evolution of resistance considerably more difficult, though not impossible. Zinc oxide (ZnO) nanoparticles and copper oxide (CuO) nanoparticles similarly exert ROS-mediated antibacterial effects and have been incorporated into wound dressings, coatings for medical devices, and nanocomposite films. The challenge in antimicrobial nanomedicine lies in achieving selective toxicity toward bacterial cells while sparing mammalian host cells a selectivity margin that is considerably narrower for inorganic species than for conventional antibiotics, and one that demands careful dose optimisation and surface engineering.

4.3 Gene Delivery and Nucleic Acid Therapeutics

The delivery of nucleic acids plasmid DNA, small interfering RNA (siRNA), and antisense oligonucleotides to defined intracellular compartments represents a demanding challenge for any carrier system. Inorganic nanoparticles offer distinct advantages in this context: they resist enzymatic degradation of the nucleic acid cargo, can be engineered with high surface-charge density for efficient condensation of polyanionic DNA/RNA, and provide a rigid scaffold that is

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more dimensionally stable than lipid-based alternatives under physiological conditions [20]. Calcium phosphate nanoparticles are of particular interest for gene delivery, as the mildly acidic pH of endosomes dissolves the CaP matrix, releasing the cargo into the cytoplasm before lysosomal degradation can occur. Carbon nanotubes, functionalised with cationic lipids or polymers, have been shown to facilitate endosomal escape through a needle-like membrane penetration mechanism, achieving transfection efficiencies in some cell types that rival those of viral vectors. Ongoing work focuses on improving endosomal escape efficiency across all inorganic platforms, as this step remains a principal bottleneck in cytoplasmic delivery.

Figure 4. Distribution of Inorganic Nanomedicine Research by Therapeutic Application Area (2010–2018)

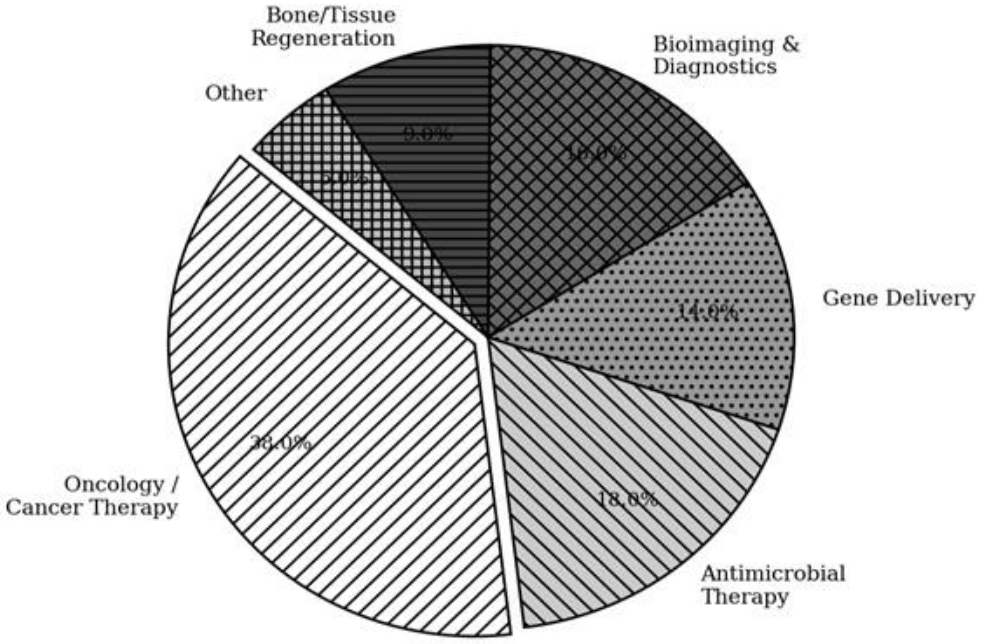

Figure 4. Distribution of inorganic nanomedicine research by therapeutic application area.

5. TOXICOLOGICAL CONSIDERATIONS AND BIOCOMPATIBILITY

No assessment of inorganic nanoparticles in nanomedicine is complete without a rigorous treatment of their toxicological profile. The very properties that render inorganic nanoparticles attractive as therapeutic platforms large surface-area-to-volume ratio, reactivity, and capacity to interact with biological macromolecules also underpin their potential to cause cellular and organismal harm. Nanoparticle toxicity is multifactorial: it depends on size, shape, surface

chemistry, dissolution rate, route of administration, dose, and the specific biological system under investigation [21]. Regulatory bodies and scientific working groups have repeatedly emphasised that the concept of a unified "nanoparticle toxicity" is a gross oversimplification; each nanoparticle composition and formulation must be characterised and evaluated independently.

Gold nanoparticles, in their colloidal form, are generally regarded as among the least cytotoxic inorganic nanomaterials, a conclusion supported by numerous cell viability and animal studies. However, cationic AuNPs particularly those functionalised with quaternary ammonium groups exhibit significant membrane disruption at low concentrations, a finding that highlights the primacy of surface chemistry over core composition in determining biological response [22]. IONPs have demonstrated an acceptable safety profile in the clinical MRI contrast agent context (several formulations have received regulatory approval), though concerns persist regarding long-term iron accumulation in hepatic and splenic tissue following repeated dosing, and the potential for Fenton reaction-mediated oxidative stress in iron-overloaded cells. Cadmium-containing quantum dots remain arguably the most toxicologically problematic class, with cadmium ion release implicated in mitochondrial dysfunction and genotoxicity; the regulatory path for QD-based therapeutics remains accordingly uncertain.

Protein corona formation the spontaneous adsorption of serum proteins onto nanoparticle surfaces in biological fluids fundamentally alters the biological identity of nanoparticles, often abrogating active targeting and accelerating opsonisation by macrophages of the mononuclear phagocyte system (MPS) [23]. Strategies to minimise corona formation include PEGylation (attachment of polyethylene glycol chains), zwitterionic surface coatings, and biomimetic cell-membrane camouflage. Standardised protocols for protein corona characterisation including hard corona composition, particle size change upon corona formation, and the relationship between corona composition and in vivo clearance half-life are still being developed by the nanomedicine research community, underscoring the immaturity of the field relative to its ambitions.

6. CHALLENGES AND FUTURE DIRECTIONS

Despite the remarkable pace of discovery in inorganic nanomedicine, the translational gap between preclinical demonstration and clinical application remains substantial. Of the thousands of inorganic nanoparticle formulations described in the peer-reviewed literature through 2018, fewer than twenty have reached clinical trials, and fewer still have received regulatory approval for therapeutic indications [24]. Several interconnected factors contribute to this disparity.

Scale-up manufacturing presents the first major challenge. Laboratory-scale syntheses, optimised for batch sizes of milligrams to grams, frequently cannot be reproduced at kilogram scales without compromising the size monodispersity, surface chemistry uniformity, and batch-to-batch consistency that regulatory quality standards demand. Green and continuous-flow synthetic

approaches are being explored to address this bottleneck, but their applicability to the full compositional range of inorganic nanoparticles has not yet been established. The second challenge relates to in vivo complexity: murine xenograft models, which dominate the preclinical literature, systematically overestimate the EPR effect relative to its prevalence in human clinical oncology, leading to unwarranted optimism in preclinical efficacy data that frequently fails to translate to human outcomes [25]. The development of more clinically predictive in vivo models including patient-derived xenografts, humanised immune system models, and three-dimensional tumour spheroid assays is a recognised priority.

A third challenge is the need for harmonised regulatory frameworks. Inorganic nanoparticles fall at the intersection of drug, device, and combination product classifications in most regulatory jurisdictions, creating uncertainty about the appropriate characterisation and testing requirements. Regulatory agencies including the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued guidance documents on the evaluation of nanotechnology-based products, but these remain non-binding and subject to case-by-case interpretation. Looking forward, the most promising near-term opportunities lie in personalised theranostic platforms that combine magnetic targeting, imaging, and chemotherapy within a single inorganic architecture, and in the integration of inorganic nanoparticles with immunotherapy for example, by co-delivering checkpoint inhibitor antibodies and photothermal agents to reprogram the tumour microenvironment [18]. Advances in machine learning-assisted materials design may further accelerate the identification of optimal nanoparticle compositions and surface formulations for specific clinical indications.

7. CONCLUSION

This review has demonstrated that inorganic chemistry provides an exceptionally rich toolkit for the design, synthesis, and functionalisation of nanoparticulate drug delivery systems. Gold nanoparticles excel in photothermal applications; iron oxide nanoparticles bridge imaging and therapeutic hyperthermia; mesoporous silica nanoparticles offer unmatched drug-loading versatility; quantum dots illuminate biodistribution in real time; and calcium phosphate platforms serve the demanding requirements of intracellular nucleic acid delivery. Across all of these systems, the interface between inorganic chemistry and biology — particularly the chemistry of surface functionalisation, stimuli-responsive linker design, and protein corona management — emerges as the critical determinant of therapeutic performance.

The data surveyed in this paper confirm that mesoporous silica platforms currently offer the highest drug-loading efficiencies (approaching 88%), while gold nanorod systems provide the greatest precision in photothermal dose deposition. The distribution of research effort, with roughly 38% focused on oncology, reflects both the magnitude of unmet clinical need in cancer

therapy and the particular suitability of inorganic nanoparticles — with their intrinsic optical and magnetic properties — to the multimodal demands of tumour treatment. Significant challenges remain in manufacturing scale-up, in vivo predictability, protein corona mitigation, and regulatory harmonisation, and these must be addressed systematically rather than treated as secondary concerns.

Ultimately, the translation of inorganic nanomedicine from laboratory promise to clinical reality will require not only advances in materials chemistry but also a deeper and more quantitative understanding of the biological pathways through which nanoparticles are distributed, retained, and cleared in complex living systems. Achieving this understanding — and building it into materials design from the outset rather than as an afterthought represents the central scientific imperative of the field as it enters its next decade of development.

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