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Review Article

Organometallic Nanoconjugates for Biomedical Imaging and Theranostics: A Molecular Engineering Perspective

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ABSTRACT

Organometallic nanoconjugates represent a transformative class of nanoscale systems uniquely positioned at the interfaces of chemistry, biology, and nanomedicine. This review provides a comprehensive molecular engineering perspective on the design, synthesis, and biomedical applications of organometallic nanoconjugates for imaging and theranostics. These hybrid constructs, which integrate organometallic cores such as gold, ruthenium, platinum, and iron with biocompatible ligands and targeting moieties, offer tunable physicochemical properties, enabling precise control over biodistribution, cellular uptake, and stimuli-responsive behaviour. The advanced engineering approaches are examined, including ligand architecture, surface functionalization, and bioconjugation techniques to enhance specificity and multifunctionality. The utility of these nanoconjugates is further explored across diverse imaging modalities, such as fluorescence, photoacoustic, MRI, CT, and PET/SPECT, emphasizing their potential for multimodal diagnostics. On the therapeutic front, applications span photothermal therapy, chemotherapy, gene delivery, and immune modulation, highlighting their versatility in combating complex diseases, such as cancer and infections. A dedicated section addresses theranostic integration, in which diagnostics and therapy are unified within a single platform for real-time monitoring and personalized treatment. Finally, future directions involving smart nanoconjugates, AI-guided design, and biosensing-enabled feedback systems are discussed, underscoring the potential of organometallic nanoconjugates in next-generation precision medicine.

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Introduction Q4

In recent decades, the integration of diagnostic and therapeutic modalities within a single nanoplatform, termed *theranostics* has revolutionized the landscape of precision medicine. Among the various nanotechnological innovations, organometallic nanoconjugates have emerged as versatile and potent candidates due to their unique hybrid architecture combining organic ligands and metal centres [1]. These nanosystems not only facilitate high-resolution imaging, but also enable targeted therapy, due to their tunable physicochemical properties, multifunctionality, and biocompatibility. These nanoconjugates have been engineered to overcome the limitations of conventional diagnostic and therapeutic agents, such as systemic toxicity, low specificity, and poor biodistribution [2]. Organometallic constructs, through molecular-level customization, address these challenges by offering site-specific targeting, controlled drug release, and real-time monitoring capabilities, making them pivotal for next-generation biomedical applications [3]. Molecular-level customization is defined as the precise modification of chemical structures and interactions at the molecular scale to optimize physicochemical stability, bioavailability, and therapeutic efficacy. This ability enables the development of systems specifically tailored to address challenges, such as poor solubility, limited permeability, and uncontrolled drug release. This review provides a comprehensive and structured overview of organometallic nanoconjugates from a molecular engineering perspective, encompassing their design principles, synthetic strategies, and functional versatility in imaging and therapy. The scope includes an in-depth exploration of organometallic components, such as gold, platinum, ruthenium, and iron, highlighting their relevance in clinical and preclinical contexts. Special emphasis is placed on molecular engineering approaches such as ligand surface functionalization, bioconjugation techniques, and stimuli-responsive modifications [4]. The objectives are to (i) systematically classify organometallic nanoconjugates based on their structural and functional properties, (ii) critically analyze their applications in various imaging modalities and therapeutic strategies, and (iii) elucidate their role in integrated theranostic platforms, ultimately guiding future innovations in smart nanomedicine [5]. Organometallic nanoconjugates represent a paradigm shift in the development of multifunctional nanosystems for use in biomedical imaging and theranostics. Their significance lies in the synergistic interaction between the metal core and functionalized organic moieties, which enables enhanced imaging contrast, selective targeting, and controlled therapeutic release. For instance, gold- and iron-based nanoconjugates are extensively utilized for photoacoustic imaging and magnetic resonance imaging (MRI), respectively, whereas ruthenium and platinum derivatives show promising anticancer activity through photodynamic and chemotherapeutic mechanisms [6]. These systems bridge the gap between diagnosis and treatment by allowing

real-time visualization of disease progression and simultaneous therapeutic intervention, thereby minimizing off-target effects and improving patient outcomes. With advancements in molecular engineering, organometallic nanoconjugates are poised to play a central role in personalized medicine by offering tailored solutions for complex diseases such as cancer, neurological disorders, and infectious conditions [7]. Organometallic nanoconjugates are characterized by their dual chemical identities, merging organic ligands with metal centres for molecular programmability and multifunctionality. This platform allows the incorporation of therapeutic agents, targeting ligands, and imaging probes, overcoming the limitations of conventional drugs by enhancing pharmacokinetics and enabling site-specific accumulation. Stimuli-responsive designs ensure spatiotemporal precision in action. These constructs are considered transformative in nanomedicine, expanding drug design and enabling advancements in theranostics, precision oncology, and biomedical imaging through rationally engineered, multifunctional systems [8]. However, challenges such as potential toxicity, long-term accumulation of heavy metals, and lack of clinical translation remain.

Overview of Organometallic Nanoconjugates

Organometallic nanoconjugates represent a unique and rapidly advancing class of hybrid nanosystems that integrate the versatile chemistry of organometallic compounds with the structural advantages of nanomaterials. Organometallic nanoconjugates are broadly defined as nanoscale platforms that incorporate one or more metal centres directly bonded to organic ligands within a nanosystem, enabling precise control of functionality, reactivity, and biological interactions [9]. Structural components typically comprise a metal core or cluster (e.g., nanoparticles of gold or iron oxide), an organic or polymeric shell, and surface-bound ligands, often engineered for stability, solubility, and targeting capabilities. These modular components allow the customization of nanoconjugates for specific biomedical purposes, including imaging, therapy, or both [8].

Figure 1 shows a schematic representation of several functional moieties that can be coupled to organometallic nanocarriers for theranostic applications. They include antibodies, small molecules, aptamers, diabodies, proteins, fluorescent probes, and therapeutic drugs. Additionally, both chelator-based and non-chelator-based radiolabeling approaches are depicted, highlighting the versatility of organometallic nanoconjugates in targeted drug delivery, imaging, and radiotherapy. A wide range of metal elements has been exploited in the design of these nanoconjugates, each offering distinct properties suitable for biomedical applications.

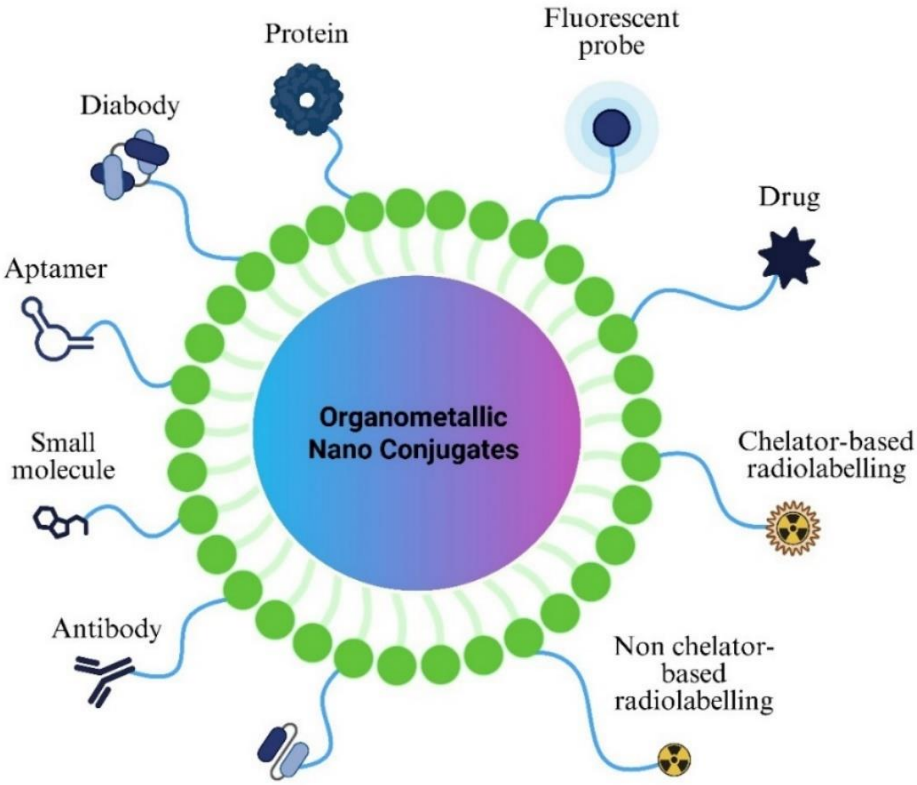

Figure 1. Structural representation of organometallic nanoconjugates showing common functional groups used for imaging and therapy

Gold (Au) is one of the most widely studied materials due to its biocompatibility, ease of surface modification, and excellent optical properties, which are conducive to imaging and photothermal therapy [10]. Ruthenium (Ru)-based complexes are of particular interest because of their redox activity and photophysical properties, making them promising platforms with clinically relevant potential for photodynamic therapy and fluorescence imaging [11]. Platinum (Pt), especially in the form of cisplatin-like complexes, is valued for its chemotherapeutic efficacy, and its conjugation to nanosystems can reduce systemic toxicity while enhancing tumor targeting [12]. Iron (Fe), typically in the form of superparamagnetic iron oxide nanoparticles (SPIONs), plays a dual role as both a drug carrier and magnetic resonance imaging (MRI) contrast agent [13]. Additionally, other transition metals such as iridium, cobalt, and gadolinium are gaining traction due to their unique redox, catalytic, and imaging functionalities [14].

Researchers design organometallic nanoconjugates based on rational coordination chemistry and nanofabrication principles rooted in coordination chemistry and nanofabrication techniques. Bottom-up strategies, such as wet chemical synthesis or self-assembly, are frequently employed to produce uniform nanoparticles, followed by conjugation with organometallic complexes or therapeutic agents. Covalent conjugation methods, including click chemistry, carbodiimide coupling, and thiol–gold interactions, are commonly used to anchor ligands or bioactive molecules onto nanoparticle surfaces [8]. Additionally, supramolecular interactions, such as host–guest chemistry and electrostatic adsorption, enable reversible or stimuli-sensitive conjugation for

controlled release. Research has shown that optimizing these synthetic strategies not only enhances the colloidal stability and functional density of nanoconjugates, but also tailors their pharmacokinetics and biodistribution profiles. For instance, PEGylated ruthenium-gold nanohybrids have demonstrated improved tumor accumulation and minimized off-target toxicity compared to free ruthenium complexes [15]. The physicochemical properties of organometallic nanoconjugates are crucial determinants of their biomedical applications. Parameters such as the particle size, shape, surface charge, hydrophobicity, and redox potential influence cellular uptake, circulation time, immune evasion, and intracellular trafficking. Spherical particles within the size range of 10–100 nm are generally preferred for tumor targeting due to the enhanced permeability and retention (EPR) effect. Surface modifications such as PEGylation or zwitterionic coatings can prevent rapid clearance by the mononuclear phagocyte system (MPS), thereby prolonging systemic circulation. Additionally, the optical properties (e.g., plasmon resonance in gold nanoparticles) and magnetic responses (as seen with iron oxide cores) facilitate their use in various imaging modalities [16]. Recent studies have highlighted that the redox-sensitive behaviour of ruthenium and platinum nanoconjugates can be exploited for site-specific drug release in acidic and oxidative tumor microenvironments, thus amplifying therapeutic outcomes while minimizing systemic side effects [17]. The integration of organometallic chemistry into nanoconjugates offers a powerful platform for advancing biomedical imaging and therapy. The diversity of metal selection, surface engineering, and conjugation strategies enables tailored functionality for specific clinical needs. Ongoing research continues to push the boundaries of their design, particularly toward stimuli-responsive, targeted, and multimodal systems, thereby setting the stage for next-generation theranostic applications [16].

Table 1. Comprehensive overview of organometallic nanoconjugates for biomedical theranostics Q5

Element/ Complex Used	Structural Characteristics	Synthesis/Conjugation Strategy	Nanoconjugate Type	Physicochemical Properties	Biomedical Relevance	Distinct Advantages	Potential Drawbacks	Ref.
Gold (Au)	Core–shell, dendrimer-linked, spherical/ nanorods	Citrate reduction, seed-mediated growth, PEGylation	AuNPs, Au-organometallic hybrids	High stability, biocompatibility, easy surface functionalization, strong SPR	Photothermal therapy, Optical imaging	Excellent biocompatibility, chemical inertness, facile surface functionalization, strong plasmon resonance for imaging and photothermal therapy	Poor biodegradability, risk of long-term tissue accumulation	[18]

Ruthenium (Ru)	Octahedral coordination, arene-Ru complexes	Microwave-assisted synthesis, ligand exchange, click chemistry	Ru(II)/Ru(III)-based nanoconjugates	Redox activity, luminescence, photoactivation potential	PDT, Nuclear imaging, Gene delivery	Rich redox chemistry, tunable photophysical properties, effective in photodynamic therapy, lower systemic toxicity than Pt drugs	Stability issues in physiological environments, potential off-target reactivity	[19]
Platinum (Pt)	Pt(IV)/Pt(II) prodrug-based, DNA-binding moieties	Co-precipitation, polymer conjugation, PEGylation	Cisplatin or Pt-conjugated NPs	High cytotoxicity, controlled release in reductive environment	Chemotherapy, Dual therapy	Established anticancer activity via DNA binding, potent apoptosis induction, well-studied mechanisms	Drug resistance, nephrotoxicity, systemic toxicity	[20]
Iron (Fe)	Fe_3O_4 or Fe_2O_3 magnetic core, core-shell structures	Co-precipitation, sol–gel, surface coating with silanes	Superparamagnetic iron oxide NPs (SPIONs)	Magnetic responsiveness, stability, surface functionalization	MRI, Magnetic hyperthermia	Strong magnetic properties for MRI and magnetic drug targeting, essential biological element with good tolerance at low doses	Risk of oxidative stress via Fenton reaction, dose-dependent toxicity	[21]
Gallium (Ga)	Ga(III) coordination complexes	Ligand coordination, encapsulation in liposomes	Ga-complex loaded NPs	Anti-proliferative, transferrin-targeting	Anticancer, Antimicrobial	Mimics iron metabolism, interferes with tumor cell iron uptake,	Limited clinical data, possible off-target effects on normal	[22]

						antimicrobial and anticancer potential	iron-dependent pathways	
Technetium (Tc)	Tc-99m radiolabeled conjugates	Chelation with ligands (DTPA, HYNIC), kit formulation	Radiolabeled nanoconjugates	Radiostability, high gamma emission, selective uptake	SPECT imaging, Tumor localization	Widely used in nuclear medicine, excellent gamma emitter for SPECT imaging, diverse coordination chemistry	Short half-life of isotopes, limited therapeutic applications, radiation safety concerns	[23]
Silver (Ag)	Spherical, prism, or wire-shaped nanostructures	Green synthesis, chemical reduction	AgNPs/Ag-organometallic complexes	Antibacterial, ROS generation, conductivity	Antimicrobial, Drug delivery	Strong antimicrobial properties, potential anticancer activity, plasmonic features for imaging	Cytotoxicity to healthy cells, risk of argyria, limited long-term biocompatibility	[24]
Iridium (Ir)	Cyclometalated complexes	Ligand substitution, photoligation	Ir(III) nanoconjugates	High photoluminescence, tunable oxidation states	Bioimaging, PDT	Exceptional photophysical properties (phosphorescence, singlet oxygen generation), promising for photodynamic therapy	Scarcity and high cost, relatively less explored in vivo biocompatibility	[25]
Copper (Cu)	Cu(I)/Cu(II) complexes, core-shell	Solvothermal, reduction in presence of ligands	CuNPs, Cu-organic hybrids	Antioxidant, ROS-based cytotoxicity	Anticancer, Antimicrobial	Redox-active, essential trace element, useful in PET	Instability in physiological conditions, risk of	[26]

						imaging with Cu isotopes, potential for catalytic cancer therapy	oxidative stress and toxicity	
Zirconium (Zr)	Zr–phthalocyanine or Zr–porphyrin complexes	Coordination with ligands, self-assembly	Zr-based nanoconjugates	Strong coordination, high thermal stability	Targeted PDT, Imaging	Excellent for PET imaging with Zr-89, strong coordination with chelators for antibody labeling	Long half-life may cause prolonged radiation burden, limited therapeutic activity	[27]

Molecular Engineering Approaches Q4

The successful application of organometallic nanoconjugates in biomedical imaging and theranostics depends significantly on advanced molecular engineering strategies. These approaches determine the physicochemical behaviour, biological interactions, targeting specificity, and multifunctionality of nanoconjugates. Key components include ligand design, surface modification, targeting strategies, bioconjugation techniques, and stimuli-responsive features that can be tailored for controlled and precise delivery in complex biological environments [28].

Ligand design and surface functionalization Q4

Ligand design and surface functionalization are fundamental for the biomedical performance of organometallic nanoconjugates. Tailoring ligands at the nanoscale level enables enhanced colloidal stability, selective biodistribution, and reduced off-target toxicity. Surface ligands include small molecules, polymers, peptides, and oligonucleotides, each chosen to improve solubility, biocompatibility, and targeting efficiency [29,30]. Polyethylene glycol (PEG) is one of the most widely used polymers for functionalization, forming a hydrophilic corona that reduces protein adsorption and prolongs the circulation time. Studies on PEGylated AuNPs have demonstrated an increased blood half-life and reduced uptake by macrophages. Similarly, thiol and amine groups are commonly used to anchor ligands to metallic cores, particularly gold and platinum nanoparticles [31]. The synthesized ruthenium-based nanoconjugates were functionalized with folic acid to target folate receptors overexpressed in cancer cells. This modification improved the cellular uptake and photodynamic efficiency. Furthermore, hydrophobic-hydrophilic ligand combinations have shown promise in forming self-assembled micelle-like nanostructures, enhancing drug loading, and cellular permeability [32]. By strategically designing ligands, researchers can dictate particle behaviour in biological environments, enabling enhanced imaging contrast and therapeutic payload delivery, as well as minimizing immune clearance. The ongoing development of zwitterionic, peptide, and multifunctional ligands continues to advance the clinical relevance of organometallic nanoconjugates [33].

Precise design of the ligand shell through approaches such as ligand architecture, surface

functionalization, and bioconjugation plays a pivotal role in dictating the in vivo behaviour of nanoconjugates [16]. By tailoring the ligand composition, charge, and spatial arrangement, surface chemistry can be optimized to modulate biodistribution, prolong circulation time, and reduce clearance by the mononuclear phagocyte system. Hydrophilic and neutrally charged modifications, such as PEGylation, provide "stealth" properties that minimize opsonization and immune recognition. Similarly, the incorporation of targeting ligands, including peptides, antibodies, aptamers, and small molecules, facilitates receptor-mediated uptake, thereby enhancing selective accumulation at disease sites while limiting off-target effects [34]. The density and orientation of ligands regulate protein corona formation, which has downstream consequences for immune evasion, tissue specificity, and therapeutic efficacy. Collectively, rational engineering of the ligand shell serves as a central determinant of the pharmacokinetics, biocompatibility, and therapeutic performance of organometallic nanoconjugates [35]. The ligand design and surface functionalization strategies are listed in **Table 2**.

Table 2. Ligand design and surface functionalization strategies in organometallic nanoconjugates for biomedical applications

Ligand Type	Organometallic Core	Surface Functionalization Strategy	Targeting Mechanism	Stimuli Responsiveness	Biomedical Use	Research Findings	Ref.
Folic acid (FA)	Gold nanoparticles (AuNPs)	Covalent binding via PEG linker	Folate receptor-mediated targeting	pH-responsive release	Cancer imaging and therapy	Enhanced cellular uptake in HeLa cells; increased tumor accumulation	[36]
RGD peptide	Iron oxide nanoparticles	EDC/NHS coupling on carboxyl surface	Integrin αvβ3 targeting	Enzyme-triggered release	MRI-guided tumor imaging	Improved MRI contrast and tumor localization	[37]
Herceptin (anti-HER2)	Platinum-based nanocarriers	Direct antibody conjugation via thiol linkage	HER2-positive breast cancer targeting	None	Targeted chemotherapy	Selective cytotoxicity against HER2-overexpressing cells	[38]
Aptamer AS1411	Ruthenium complexes	Electrostatic interaction + PEGylation	Nucleolin-mediated internalization	Redox-sensitive release	Photodynamic therapy	Nucleus-targeted delivery with reduced off-target effects	[39]
Hyaluronic acid (HA)	Iron oxide NPs	Layer-by-layer self-assembly	CD44 receptor targeting	pH-responsive release in tumor microenvironment	MRI and drug delivery	Increased tumor-specific accumulation and enhanced imaging	[40] r40

Transferrin	Gold nanorods	Maleimide-thiol chemistry	Transferrin receptor targeting	Light-responsive photothermal effect	Theranostics	Enhanced penetration in brain tumors; multimodal imaging	[41]
Glucose	Copper-based complexes	Schiff base formation	Glucose transporter-mediated uptake	None	Tumor imaging and hypoxia detection	Selective uptake in hypoxic tumor cells	[42]
TAT peptide	Ruthenium–platinum hybrid	Click chemistry with azide groups	Cell-penetrating internalization	pH and redox dual-responsive	Antimicrobial and anticancer delivery	Broad-spectrum intracellular penetration with controllable release	[43]
Mannose	Iron oxide nanoclusters	Silanization + mannose conjugation	Mannose receptor on macrophages	Enzyme-triggered degradation	Immune-targeting and diagnostics	Enhanced uptake in macrophages, potential in TB diagnostics	[44]
Biotin	Lanthanide-based organometallics	Biotin–avidin binding system	Cancer cell internalization via biotin receptors	pH-sensitive release	Fluorescent imaging and radiotherapy	High affinity for cancer cells; image-guided therapy	[45]

Targeting strategies: Passive vs. active targeting

Targeting strategies are pivotal for directing organometallic nanoconjugates to diseased tissues, while minimizing systemic exposure. These strategies can be broadly categorized into passive and active targeting [46]. Passive targeting relies on the enhanced permeability and retention (EPR) effect observed in tumors due to their leaky vasculature and poor lymphatic drainage. Metallic nanoconjugates, particularly those in the 10–100 nm range, exploit this effect to preferentially accumulate in tumor tissues. For instance, iron oxide nanoparticles used in MRI-guided therapy have demonstrated strong passive accumulation in glioblastoma models [47]. Active targeting enhances specificity by incorporating ligands that bind to receptors overexpressed on target cells. Antibodies, peptides, and aptamers are among the most effective therapeutic agents available. In one study, gold nanoparticles functionalized with HER2-targeting antibodies selectively accumulated in HER2-positive breast cancer cells, enhancing both the imaging contrast and therapeutic efficacy [48]. Dual-targeting strategies that combine passive and active mechanisms have demonstrated a superior performance. For example, platinum-based nanoconjugates modified with RGD peptides (targeting integrins) and PEG chains exhibit improved tumor localization and deeper tissue penetration [49]. Emerging approaches include the use of biomimetic coatings such as cancer cell membranes or extracellular vesicles to enhance homotypic targeting and immune evasion. As precision medicine evolves, active targeting is expected to shift toward highly personalized ligands identified through omics technologies and AI-assisted modelling [50].

Bioconjugation techniques (antibodies, peptides, and aptamers) Q4

Bioconjugation enables the integration of biological recognition elements with metallic nanocarriers, thereby greatly enhancing their selectivity and functionality. This process involves covalently or non-covalently linked biomolecules, such as antibodies, peptides, or

aptamers, attached to the surface of organometallic nanoparticles [51]. Covalent conjugation methods, such as carbodiimide-mediated amide coupling, click chemistry, and maleimide-thiol coupling, are preferred for their stability under physiological conditions. Antibodies conjugated to gold and iron nanoparticles have been extensively explored for use in diagnostic imaging and targeted photothermal therapy. For instance, trastuzumab-functionalized gold nanorods selectively targeted HER2+ tumors in vivo, enabling both near-infrared imaging and ablation therapy [52].

Peptides, such as RGD, TAT, and GE11, have shown efficacy in targeting integrins, nuclear import mechanisms, and EGFR-expressing cells, respectively. Their small size and ease of synthesis make them attractive for high-throughput functionalization [53]. Aptamers, single-stranded DNA or RNA oligonucleotides, offer high specificity and affinity for antibodies but have better thermal stability and lower immunogenicity. AS1411 aptamer-conjugated AgNPs demonstrated enhanced nuclear targeting and cytotoxicity in colorectal cancer cells [54,55]. The choice of bioconjugation technique affects not only the targeting efficiency, but also particle stability, internalization pathways, and immune recognition. Advanced strategies, such as site-specific conjugation and bio-orthogonal reactions (e.g., strain-promoted alkyne-azide cycloaddition), are now being employed to retain biomolecule activity post-conjugation [56]. **Figure 2** illustrates three types of functionalized lipid nanoparticles: protein-conjugated nanoparticles, aptamer-conjugated nanoparticles, and antibody-conjugated nanoparticles. Each system features of a fluid lipid inner core surrounded by a lipid bilayer conjugated with specific targeting ligands: proteins (red), aptamers (blue), and antibodies (cyan). These surface modifications enhance the targeting ability of NPs in drug delivery and diagnostic applications, enabling precise interaction with biological targets.

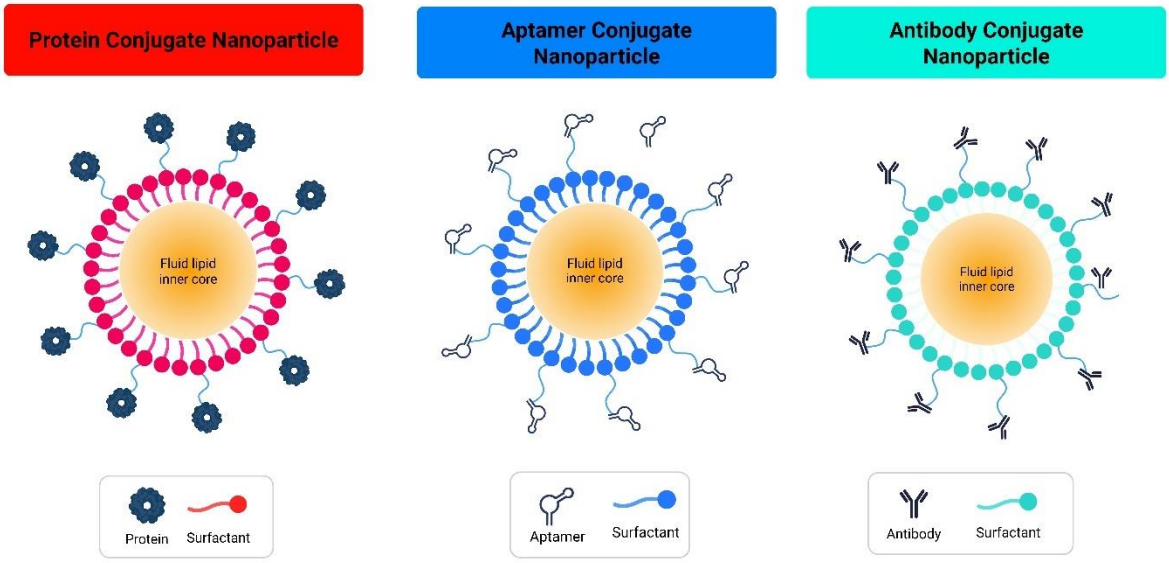

Figure 2. Schematic representation of lipid nanoparticles functionalized with biological ligands. Illustration of lipid nanoparticles conjugated with proteins, aptamers, and antibodies to enhance targeting, drug delivery efficiency, and theranostic potential

Table 3. Bioconjugation techniques employed in organometallic nanoconjugates for theranostic applications Q5

Bioconjugation Moiety	Organometallic Core	Conjugation Chemistry	Targeting Ligand	Target Biomarker	Application (Imaging/Therapy)	Outcomes	Ref.
Antibody (Trastuzumab)	Gold Nanoparticles (AuNPs)	EDC/NHS coupling	Anti-HER2	HER2 receptor (Breast Cancer)	Photoacoustic Imaging + PTT	Enhanced tumor targeting and ablation	[57]
Peptide (RGD)	Iron Oxide Nanoparticles	Maleimide-thiol click chemistry	Integrin-binding	αvβ3 Integrin (Tumor angiogenesis)	MRI + Drug Delivery	Improved vascular targeting and tumor retention	[58]
Aptamer (AS1411)	Ruthenium Complex	Electrostatic adsorption + covalent linkage	Nucleolin-binding	Nucleolin (Breast, Lung Cancer)	Fluorescence Imaging + Chemotherapy	High selectivity, reduced off-target toxicity	[59]
Antibody (Cetuximab)	Platinum-based Nanoconjugates	Amide bond via linker chemistry	EGFR	Epidermal Growth Factor Receptor	CT Imaging + Chemoradiotherapy	Synergistic diagnostic and therapeutic effects	[60]
Peptide (TAT)	Iron–Gold Hybrid NPs	Covalent amide bond	Cell-penetrating peptide	Nucleus and mitochondria	Multimodal Imaging + PDT	Improved cellular internalization and mitochondrial targeting	[61]
Aptamer (VEGF165-specific)	Iridium Complex	Click chemistry (azide-alkyne)	VEGF Receptor	Angiogenesis-associated cancers	Luminescence Imaging	Visualizes angiogenic vasculature, precise targeting	[62]
Antibody Fragment (scFv)	Gold Nanorods	Bio-orthogonal conjugation	HER2	HER2-positive breast cancer	Photoacoustic Imaging + PTT	High-resolution imaging with minimal background	[63]
Peptide (CREKA)	Iron Oxide–Gold Hybrid	Thiol-gold bond + PEG spacer	Fibrin-binding	Clotted plasma proteins in tumor vasculature	MRI + Drug Delivery	Targeted delivery to tumor-associated clots	[64]
Aptamer (MUC1-specific)	Platinum Nanoclusters	Covalent conjugation via carboxyl–amine reaction	MUC1	Breast, Pancreatic Cancer	Chemotherapy	Improved targeting efficiency and cytotoxicity	[65]
Dual-ligand (Antibody + Aptamer)	Ruthenium–Gold Core–Shell NP	Layer-by-layer conjugation	Dual: HER2 + Nucleolin	Breast Cancer	Multimodal Theranostics	Synergistic targeting and improved precision	[66]

Stimuli-responsive modifications (pH, redox, light, and enzyme)

Stimuli-responsive organometallic nanoconjugates are engineered to be selectively activated in pathological environments, offering spatiotemporal control over imaging and therapy. These systems are typically sensitive to internal stimuli (pH, redox, and enzymes) or external cues such as light, temperature, and magnetic fields [67]. pH-responsive designs exploit the acidic microenvironment of tumors (pH ~6.5) to trigger drug release or structural transformations. For example, iron oxide nanoparticles conjugated with pH-labile hydrazone linkers release doxorubicin only under acidic conditions, improving the therapeutic index and minimizing systemic toxicity [68]. Redox-sensitive systems use disulfide or selenium bonds that are cleaved in the presence of high intracellular glutathione (GSH) levels. Gold nanoconjugates with disulfide-linked siRNA demonstrate rapid release inside tumor cells, enabling effective gene silencing [69]. Light-responsive nanoconjugates, particularly those based on ruthenium and platinum complexes, have been designed for photodynamic or photothermal therapy. Upon irradiation, these systems generate reactive oxygen species (ROS) or localize heat to kill cancer cells. One notable study used near-infrared light to activate a ruthenium-photocaged complex, achieving tumor regression with minimal collateral damage [70]. Enzyme-responsive designs leverage tumor-associated enzymes MMPs and cathepsins to trigger activation. Platinum-based prodrugs functionalized with MMP-cleavable peptides have shown promising results in the selective release of active compounds in metastatic environments. These smart systems are at the forefront of personalized theranostics, where molecular cues unique to the disease microenvironment dictate activation, thereby enhancing efficacy and safety [71]. These systems are commonly engineered to respond to internal triggers such as an acidic tumor microenvironment (pH-sensitive linkages that cleave under acidic conditions), overexpressed enzymes (enzyme-cleavable bonds that release active cargo), and intracellular redox gradients (disulfide or thiol-sensitive linkers responsive to elevated glutathione levels) [72]. In parallel, they may also be designed for external activation using physical stimuli such as light (photo-cleavable bonds enabling photodynamic or photothermal effects), magnetic fields (iron-oxide cores for magnetic hyperthermia or guided delivery), or ultrasound (acoustic cavitation to trigger release) [73]. At the molecular level, these responses are incorporated through the strategic choice of metal–ligand coordination chemistry, cleavable linkers, photosensitizers, or magnetic components within the nanoconjugate framework. Such a rational design ensures spatiotemporal control over therapeutic or imaging functions, thereby enhancing precision and minimizing off-target effects [74].

Biomedical Imaging Applications Q4

Optical imaging Q4

Optical imaging modalities, particularly fluorescence and photoacoustic imaging, have advanced significantly with the advent of organometallic nanoconjugates. Fluorescence imaging benefits from the tunable photophysical properties of organometallic complexes, such as ruthenium (II), iridium (III), and gold-based compounds. These metal centres provide long emission lifetimes, high quantum yields, and resistance to photobleaching, rendering them ideal for high-resolution in vivo imaging. For instance, Ru(II)-polypyridyl complexes conjugated to targeting peptides show strong fluorescence emission and preferential tumor accumulation, enabling precise imaging of cancerous tissues [75].
Photoacoustic imaging, a hybrid modality combining optical excitation and ultrasound detection, has gained traction because of its high spatial resolution and deep-tissue penetration. Organometallic nanoparticles such as gold nanorods and nanoshells exhibit strong near-infrared (NIR) absorption and efficient

photothermal conversion, making them suitable for photoacoustic imaging. In a recent study, PEGylated gold nanorods conjugated with folic acid enabled targeted photoacoustic imaging of ovarian tumors with enhanced contrast and specificity [76]. Dual fluorescence-photoacoustic probes incorporating organometallic cores with surface modifications, such, Cy5.5 or IR780 dyes, have been designed for real-time imaging and guided therapy. Such multifunctional systems are pivotal in preclinical research, and have demonstrated potential for clinical translation. Future research should focus on optimizing quantum yields, biocompatibility, and the development of activatable probes that respond to tumor microenvironment stimuli [77].

Magnetic resonance imaging (MRI) Q4

Magnetic Resonance Imaging (MRI) remains one of the most powerful noninvasive imaging modalities due to its superior anatomical resolution and deep tissue penetration. Organometallic nanoconjugates, especially those incorporating paramagnetic metals, such as gadolinium (Gd), manganese (Mn), and iron (Fe), have been engineered to enhance MRI contrast and specificity. These metals exhibit unpaired electrons, which enhance the relaxation rates of the surrounding water protons and improve the image clarity [78]. Iron oxide nanoparticles (SPIONs), when functionalized with organometallic ligands or therapeutic agents, offer T2-weighted contrast, and have been extensively studied for brain tumor and liver imaging. For instance, Fe_3O_4 nanoparticles conjugated with PEG and RGD peptides enabled the active targeting of glioblastoma and enhanced the T2 signal in murine models. Similarly, Mn-based organometallic chelates integrated into mesoporous silica nanocarriers have demonstrated excellent T1 contrast enhancement and high biocompatibility [79]. Gadolinium-based organometallic nanoconjugates face challenges due to nephrotoxicity concerns. However, recent efforts to encapsulate Gd-chelates within biocompatible nanostructures or to use dual-modal Gd-Au systems have mitigated toxicity, while enabling both MRI and CT contrast [80]. Multifunctional MRI agents incorporating therapeutic moieties (e.g., doxorubicin and siRNA) within the organometallic framework allow for theranostic applications, enabling simultaneous drug delivery and real-time monitoring of therapeutic outcomes. The combination of tumor-specific ligands (e.g., transferrin or HER2 antibodies) with organometallic MRI agents further improves target specificity [81]. Research is increasingly focusing on responsive MRI agents that are activated under tumor microenvironment conditions, such as pH or redox potential, thereby enhancing the specificity and sensitivity of tumor imaging [82].

Computed tomography (CT)

Computed Tomography (CT) relies on X-ray attenuation to produce high-resolution anatomical images. Organometallic nanoconjugates, particularly those incorporating high atomic number (Z) metals such as gold (Z = 79), bismuth (Z = 83), and tantalum (Z = 73), serve as potent CT contrast agents due to their excellent X-ray attenuation capabilities. Compared to traditional iodine-based agents, metal-based nanoconjugates offer prolonged circulation, enhanced tissue retention, and reduced toxicity [83]. Gold nanoparticles (AuNPs) are the most widely studied organometallic CT agents. Their surfaces can be easily functionalized with targeting ligands, polymers, or therapeutic payloads, thereby enabling dual imaging and therapy. For example, PEGylated AuNPs conjugated with anti-EGFR antibodies have shown superior contrast enhancement in head and neck tumor models along with prolonged retention in tumor vasculature [84]. Recent research has explored core-shell structures such as $Au@SiO_2$ and $Au@Bi_2S_3$ for enhanced CT contrast and synergistic therapeutic effects. These nanoconjugates not only improve the imaging depth and resolution, but also serve as carriers for photothermal therapy. Additionally,

bismuth sulfide nanoparticles have demonstrated high contrast in CT imaging with low toxicity, thus offering alternatives to traditional gold systems [85]. Dual-modal CT/photoacoustic and CT/MRI agents that integrate organometallic components are emerging as key players in precision diagnostics. For instance, Wang et al. (2022) developed a Gd-Au nanoconjugate for combined MRI and CT imaging in liver cancer models, allowing detailed anatomical and functional assessments [86]. The ongoing challenge remains the balance between contrast efficacy, clearance, and long-term safety, which is being addressed through biodegradable and renally clearable nanoparticle designs.

Nuclear imaging (PET/SPECT)

Positron Emission Tomography (PET) and single-photon emission computed tomography (SPECT) are highly sensitive nuclear imaging techniques that enable the quantitative visualization of biological processes at the molecular level. Organometallic nanoconjugates are ideal platforms for these modalities due to their ability to stably incorporate radionuclides such as technetium-99m (^99mTc), gallium-68 (^68Ga), copper-64 (^64Cu), and zirconium-89 (^89Zr) [87]. Organometallic cores provide structural stability and functional versatility, allowing the integration of radiometals through chelation or direct binding. For example, ^64Cu-labeled dendrimer-based platinum conjugates have been developed for PET imaging of metastatic tumors, providing both diagnostic insights and chemotherapeutic delivery. Similarly, ^99mTc-labeled AuNPs functionalized with HER2-specific peptides demonstrated high affinity toward breast cancer cells, enabling SPECT imaging with high tumor-to-background ratios [88]. Dendrimers, a sophisticated nanoscale concept, are transforming cancer treatment by tackling the critical challenges associated with conventional therapies, including poor drug solubility, systemic toxicity, oral bioavailability, side effects, and drug resistance therapy. These branched molecular frameworks serve as attractive drug delivery nanocarriers, with their engineered structure enabling the controlled release and targeted delivery of chemotherapeutic agents [89]. Chelators, such as DOTA, NOTA, and DTPA, are commonly employed to link radionuclides with organometallic nanoparticles. The design of multifunctional nanoconjugates allows for dual imaging and therapy, as exemplified by ^89Zr-labeled hafnium oxide nanoparticles, which also function as radiosensitizers for enhanced radiotherapy in gliomas. Research is also advancing toward click chemistry-based radiolabeling, enabling efficient and site-specific conjugation of radionuclides under mild conditions and improving radiochemical purity and biological stability. Due to the high sensitivity of PET/SPECT, challenges remain in terms of radionuclide half-life matching, radiation dose management, and regulatory approval. Nevertheless, organometallic nanoconjugates accelerate the integration of nuclear imaging into personalized medicine and theranostics [90].

Multimodal imaging systems

Multimodal imaging leverages the strengths of different imaging techniques, such as optical, magnetic, nuclear, and acoustic imaging, to overcome the limitations of single modalities and provide a comprehensive understanding of disease states. Organometallic nanoconjugates offer an ideal scaffold for designing multimodal probes due to their tunable physicochemical properties, multivalent surface functionality, and compatibility with various imaging agents [91]. Gold-based nanoconjugates have been successfully developed for trimodal imaging by combining CT, photoacoustic, and fluorescence imaging. For instance, folic acid-conjugated $Au@SiO_2$ core-shell nanoparticles integrated with NIR dyes have allowed real-time tracking and high-resolution visualization of tumor margins during surgery. Similarly, iron oxide-gold hybrid nanoparticles functionalized with PEG and radiolabeled with ^64Cu provide both MRI and PET capabilities for glioma imaging [92]. Another example is the use of gadolinium-ruthenium conjugates for MRI and fluorescence

dual imaging, enabling detailed anatomical visualization along with subcellular localization. Researchers have also employed manganese-based coordination polymers combined with indocyanine green for pH-sensitive MRI-fluorescence bimodal imaging in acidic tumor environments [93]. Multimodal platforms facilitate image-guided therapy by offering dynamic and real-time insights into biodistribution, targeting efficiency, and therapeutic outcomes. These hybrid systems are particularly valuable in precision oncology, where preoperative planning and intraoperative guidance are critical [94]. Future directions involve integrating biosensing functions and artificial intelligence to further enhance image interpretation and prediction of therapeutic responses. Despite the synthetic complexity and regulatory hurdles, multimodal organometallic nanoconjugates represent the next frontier in personalized image-guided theranostics.

Therapeutic Applications in Nanomedicine

Organometallic nanoconjugates have emerged as potential tools in nanomedicine due to their modular design, multifunctionality, and capacity to respond to biological cues. Their ability to combine therapeutic and diagnostic functionalities in a single nanosystem uniquely positions them in advanced treatment modalities. In this section, we discuss the various therapeutic applications of these nanoconjugates [95].

Photothermal and photodynamic therapy

Organometallic nanoconjugates are highly effective in photothermal therapy (PTT) and photodynamic therapy (PDT), due to their unique photophysical properties. In PTT, nanoconjugates, such as gold nanorods or nanoshells, convert near-infrared (NIR) light into heat, inducing localized tumor ablation. The use of gold-based organometallic conjugates modified with indocyanine green (ICG), demonstrated enhanced photothermal conversion and tumor suppression in vivo [96]. In PDT, the generation of reactive oxygen species (ROS) upon light activation is critical. Ruthenium-based organometallic complexes are well-known photosensitizers due to their ability to generate singlet oxygen (^1O2). A previous study employed a ruthenium(II)-bipyridine complex conjugated with a targeting peptide to achieve effective mitochondrial localization and induction of apoptosis in breast cancer cells [97]. Importantly, dual-mode PDT/PTT platforms have been developed to overcome the limitations of oxygen deficiency in tumor tissues. A notable example is platinum (IV) complexes conjugated to carbon nanodots, offering synergistic ROS production and hyperthermia under NIR irradiation. These systems not only enhance cytotoxicity but also reduce side effects compared to conventional chemotherapy [98]. Organometallic nanoconjugates offer tunable photophysical behaviour, deep tissue penetration (particularly in the NIR region), and precise targeting capabilities, making them ideal candidates for advanced phototherapy applications in cancer.

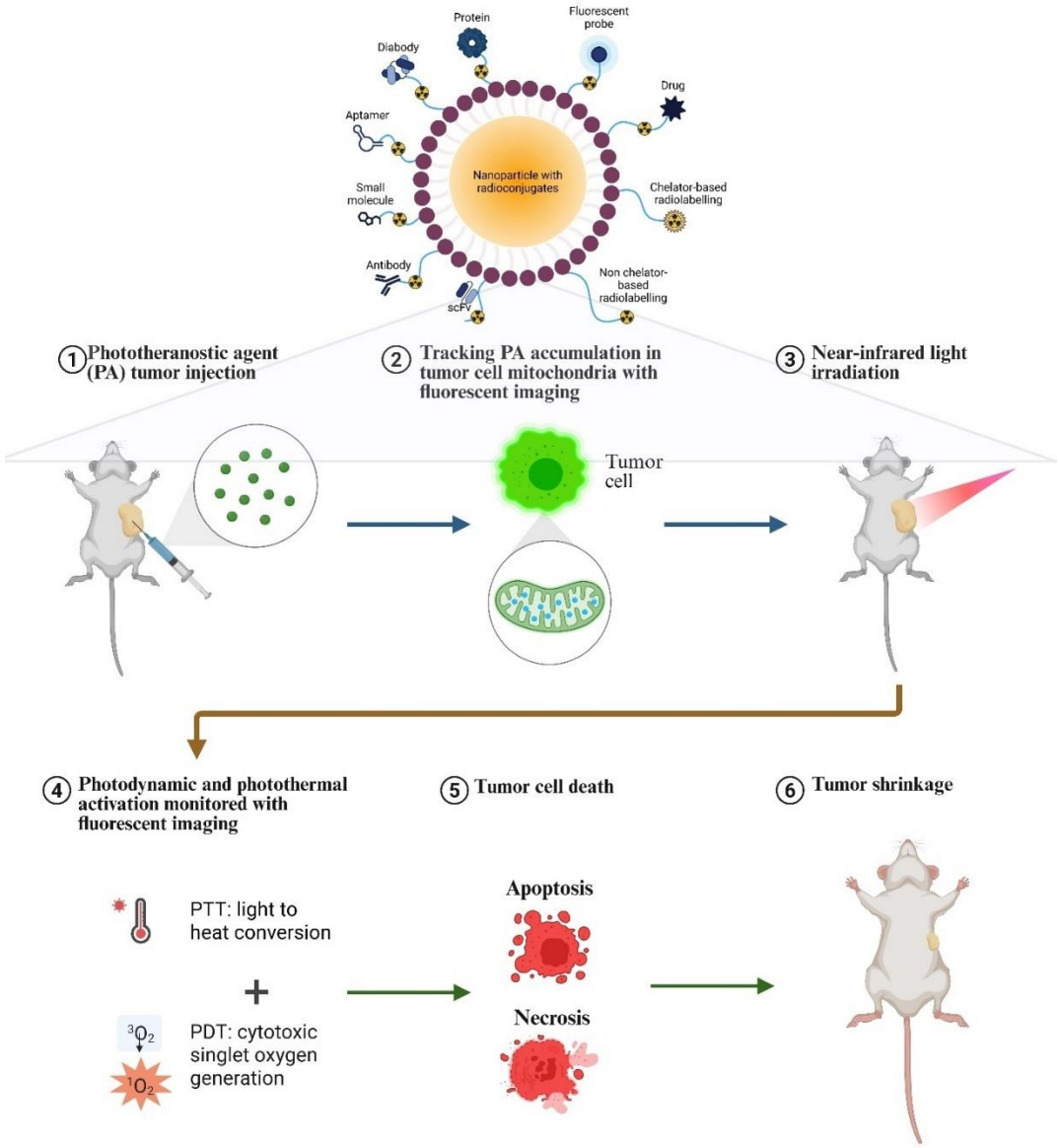

Figure 3. Mechanism of organometallic nanoconjugates-based phototheranostics for tumor imaging and treatment

Figure 3 demonstrates the stepwise process of phototheranostic intervention using multifunctional nanoparticles conjugated with targeting ligands, such as aptamers, antibodies, and proteins, and radiolabels for precise tumor targeting. Initially, a phototheranostic agent (PA) was injected directly into the tumor site (Step 1), allowing mitochondrial accumulation in the tumor cells, which was visualized through fluorescent imaging (Step 2). Near-infrared (NIR) light irradiation (Step 3) triggers both photothermal therapy (PTT), which converts light into localized heat, and photodynamic therapy (PDT), which generates reactive singlet oxygen species (Step 4). These synergistic effects lead to tumor cell apoptosis and necrosis (Step 5), ultimately resulting in tumor shrinkage (Step 6).

Chemotherapy and drug delivery

Organometallic nanoconjugates provide a platform for the site-specific delivery of chemotherapeutic agents, enhancing efficacy and minimizing systemic toxicity. These systems exploit the high surface area of nanoscale carriers, allowing for high drug-loading efficiency and sustained-release profiles [99,100]. Cisplatin and its derivatives are the cornerstones of organometallic chemotherapies. Recent innovations involve the conjugation of platinum (IV) prodrugs to nanocarriers for redox-triggered intracellular activation. For example, Li et al. (2021) reported a Pt(IV)-prodrug-loaded dendrimer decorated with folic acid for targeted drug delivery in ovarian cancer, exhibiting enhanced cellular uptake and tumor regression in murine models [101]. Gold nanoparticles (AuNPs) functionalized with doxorubicin via pH-sensitive linkers have also shown promise in drug-resistant cancers. Upon endosomal acidification, the linkers degrade, releasing doxorubicin specifically within tumor cells. Kumar et al. (2020) highlighted the superior tumor penetration and reduced cardiotoxicity of such conjugates in a mouse xenograft model of triple-negative breast cancer [102]. Dual-drug-loaded systems have been designed using organometallic platforms such as co-loading paclitaxel and cisplatin on iron oxide nanoparticles. These formulations demonstrate synergistic antitumor effects and allow magnetic targeting for localized drug accumulation [103]. Organometallic nanoconjugates offer multifunctional capabilities including real-time imaging, controlled drug release, and combinatorial therapy. Their tunable pharmacokinetics, biodegradability, and targeting versatility make them next-generation drug delivery vehicles in oncological settings [104].

Gene and nucleic acid delivery

Organometallic nanoconjugates have also revolutionized gene therapy by overcoming the limitations of viral vectors, such as immunogenicity and low loading capacity. Their metal-core frameworks and surface modifiability allow for stable encapsulation or conjugation of genetic materials, including siRNA, miRNA, and plasmid DNA [105]. Iron oxide nanoparticles coated with polyethyleneimine (PEI) and conjugated with gold nanoclusters have been used for dual magnetic and gene delivery purposes. The hybrid system demonstrated efficient siRNA delivery to silence VEGF expression in glioblastoma cells, leading to significant inhibition of tumor growth [106]. Ruthenium and cobalt complexes have also been explored for DNA binding because of their planar aromatic ligands, which intercalate into the DNA grooves. A previous study introduced a Ru (II)-polypyridyl complex attached to a lipid-based nanocarrier for miRNA delivery. This system facilitates efficient nuclear translocation and enables real-time fluorescence tracking of gene release [107]. Stimulus-responsive systems have also been designed using organometallic nanoconjugates. For example, platinum-based nanoconjugates that release DNA under reductive intracellular conditions have shown promise in cancer immunomodulation. These constructs protect nucleic acids from nuclease degradation and improve the gene transfection efficiency [108]. In gene delivery, the nanoconjugate surface can be functionalized with cationic or nucleic acid-binding ligands, while the organometallic core contributes to structural stability, facilitates condensation of genetic cargo, and in some cases, provides redox activity that aids in controlled release within the intracellular environment [109]. In immune modulation, the unique physicochemical properties of metal centres that catalyse the generation of reactive oxygen species, redox signalling, or presentation of immunogenic metal-ligand motifs can influence dendritic cell activation, cytokine release, or tumor microenvironment reprogramming. Thus, the organometallic core not only serves as a scaffold but also actively participates in shaping therapeutic outcomes by providing catalytic, redox, and structural functionalities that complement the engineered surface features of the nanoconjugate [110]. Organometallic nanoconjugates offer a versatile

platform for precise and safe nucleic acid delivery, with the added advantages of multimodal imaging and stimuli-sensitive release, enhancing their potential for personalized cancer therapies.

Immunotherapy synergies

The integration of organometallic nanoconjugates with immunotherapy represents a transformative approach in cancer treatment, enabling the modulation of immune responses along with direct tumor targeting. These nanoconjugates can act as delivery vehicles for immune adjuvants, checkpoint inhibitors, or antigenic peptides, thereby improving the immunogenicity of tumors [111]. AuNPs have been employed to deliver anti-PD-L1 antibodies in a spatiotemporally controlled manner. For instance, researchers have developed a gold-based nanoconjugate functionalized with an anti-PD-L1 antibody and pH-sensitive linker, achieving significant tumor regression in melanoma models via enhanced T-cell infiltration [112]. Ruthenium complexes, due to their ROS-generating capacity, have also been used to induce immunogenic cell death (ICD), thereby triggering dendritic cell activation and subsequent T-cell priming. A 2023 study demonstrated that a Ru(II)-based nanoconjugate, when combined with a toll-like receptor agonist, resulted in amplified systemic immune responses and durable tumor immunity [113].

Table 4. Immunotherapy synergies using organometallic nanoconjugates: mechanistic insights and therapeutic outcomes Q5

Organometallic Core	Surface Ligand / Cargo	Immunotherapy Type	Target Immune Component	Mechanism of Action	Cancer Type / Model	Therapeutic Outcome	Ref.
Gold (Au) NPs	Anti-PD-L1 antibody + PEG	Immune checkpoint blockade	PD-L1/PD-1 axis	Enhanced T-cell activation and tumor immune infiltration	Melanoma (B16F10)	Increased CD8+ T cell response; tumor suppression	[114]
Iron Oxide NPs	CpG ODN (TLR9 agonist)	Immune stimulation	Dendritic cells (TLR9)	Activation of DCs → Th1 response → T-cell priming	Breast cancer (4T1)	Delayed tumor growth, systemic immunity	[115]
Platinum (Pt) NPs	Cisplatin + anti-CD47	Immune evasion blockade	CD47-SIRPα axis	Promotes phagocytosis by macrophages; induces immunogenic cell death	Ovarian carcinoma	Synergistic cytotoxic and immune effect	[116]
Ruthenium-based complex	CpG + photosensitizer	Photo-immunotherapy	TLR9 and ROS-mediated ICD	Combines ROS-induced damage with immune activation	Colon cancer (CT26)	Tumor regression, memory T cell response	[117]
Copper sulfide (CuS) NPs	IL-2 + Photothermal agent	Cytokine-mediated immunotherapy	T cell expansion (via IL-2)	Local photothermal ablation + systemic T cell stimulation	Lung cancer (LLC1)	Enhanced T cell infiltration and tumor shrinkage	[118]

Gold nanorods	Tumor-associated antigen + GM-CSF	Cancer vaccine strategy	Antigen-presenting cells	Induces DC maturation and tumor antigen-specific response	Pancreatic cancer	Long-term immunity; reduction in metastasis	[119]
Iron-platinum alloy NPs	siRNA (PD-L1 silencing) + DOX	Gene-immuno combo therapy	Tumor cells + immune checkpoint	PD-L1 knockdown + DOX-induced ICD	Triple-negative breast cancer	Potent immune reactivation + tumor control	[120]
Silver NPs	TLR agonists + HER2 peptide	Innate-adaptive immune bridging	TLR7/8, HER2+ cells	Combines innate immune priming and tumor antigen presentation	HER2+ breast cancer	Vaccine-like immune protection	[121]
Titanium dioxide (TiO_2) NPs	Antigen + adjuvant (Poly I:C)	Cancer nanovaccine	Dendritic cells	Endosomal antigen presentation and cytokine release	Prostate cancer	Strong CTL activation and tumor reduction	[122]
Zinc-based MOFs	Anti-CTLA-4 + IL-12	Combination checkpoint & cytokine	CTLA-4 blockade + Th1 cytokine	Reverses Treg suppression; promotes Th1/CTL activation	Melanoma (B16)	Prolonged survival; immunological memory	[123]

Additionally, platinum and iron oxide nanoconjugates have shown efficacy in reprogramming tumor-associated macrophages (TAMs) from an immunosuppressive M2 phenotype to a pro-inflammatory M1 phenotype. Such reprogramming augments antitumor immunity and enhances the efficacy of checkpoint blockade therapies. Organometallic nanoconjugates, therefore offer synergistic opportunities in immunotherapy by enabling combination regimens, enhancing tumor immunogenicity, and providing real-time monitoring of immune responses, paving the way for adaptive and personalized treatment paradigms [124].

Anti-microbial and anti-biofilm strategies

Beyond oncology, organometallic nanoconjugates have proven effective in the treatment of microbial infections and biofilm-associated diseases. Their multitarget mechanisms, such as membrane disruption, DNA binding, and ROS generation, provide a robust approach for overcoming microbial resistance [125]. Silver-based organometallic conjugates have been widely studied for their antimicrobial efficacy. A recent report by Sharma et al. (2022) demonstrated that AgNPs conjugated with antibiotics such as vancomycin exhibited synergistic antibacterial activity against multidrug-resistant Staphylococcus aureus, including biofilm eradication at sub-MIC levels [126]. Gold- and platinum-based nanoconjugates have also shown potent antibiofilm activity. In one study, AuNPs functionalized with cationic peptides penetrated bacterial biofilms and released nitric oxide, disrupting the biofilm matrix and enhancing antibiotic sensitivity. This strategy proved effective against Pseudomonas aeruginosa biofilms in chronic wound models [127]. Iron oxide-based nanoconjugates have been integrated with photodynamic antimicrobial therapy (aPDT), in which ROS generation under light triggers bacterial membrane lysis. This dual-action system exhibited high efficacy against Gram-positive and Gram-negative pathogens with minimal cytotoxicity to mammalian cells [128].

Integration of Theranostics

Principles and advantages of theranostics

Theranostics, derived from "therapy" and "diagnostics," refers to the integrated approach that combines diagnostic imaging and therapeutic interventions into a single nanoplatform. This paradigm shift addresses the limitations of conventional cancer treatment strategies, which often lack specificity, real-time monitoring, and adaptability. Organometallic nanoconjugates, with their multifunctional capabilities, play a central role in advancing theranostic systems by enabling targeted delivery, enhanced imaging contrast, and controlled drug release [129]. The key principle involves engineering nanoparticles that can simultaneously image the tumor environment (e.g., via MRI, PET, or optical imaging) while delivering therapeutic agents, such as chemotherapeutic drugs or photothermal agents. Organometallic cores such as gold (Au), iron oxide (Fe_3O_4), and ruthenium (Ru) offer unique optical, magnetic, and catalytic properties that are harnessed for dual functionality [130]. Reported gold–iron oxide hybrid nanostructures are functionalized with folate ligands for targeted imaging and photothermal ablation of breast cancer. This dual-function design enables high-resolution MRI imaging and thermal therapy under NIR light, with excellent tumor specificity and minimal systemic toxicity. Such integrated systems improve treatment accuracy, allow real-time feedback, and reduce off-target effects [131]. The theranostic approach is particularly impactful in personalized medicine, where treatment is tailored based on an individual's disease characteristics and real-time therapeutic response. It enhances clinical decision making by allowing physicians to monitor drug efficacy, biodistribution, and possible resistance mechanisms [132]. Organometallic theranostics hold great promise in precision oncology because they enhance treatment outcomes, minimize side effects, and enable the longitudinal tracking of disease progression [133]. A gold-iron oxide organometallic nanoconjugate can be engineered with dual functionality, where the iron oxide core provides MRI contrast to enable real-time monitoring of tumor accumulation, while the gold component acts as a photothermal transducer. Once MRI confirms selective accumulation of the nanoconjugate at the tumor site, an external near-infrared light stimulus can be applied to activate the gold core, producing localized hyperthermia and tumor ablation [134]. A ruthenium-based nanoconjugate functionalized with a photosensitizer could allow fluorescence imaging to guide biodistribution, and upon achieving sufficient tumor localization, controlled light exposure could trigger photodynamic therapy. Such an integrated design ensures that diagnostic information directly informs therapeutic activation, thereby achieving precision, reducing systemic toxicity, and exemplifying the clinical value of theranostic nanoconjugates [135].

Dual-function and multifunctional nanoconjugates

Dual-function nanoconjugates integrate two core capabilities, diagnostic and therapeutic, within a single nanosystem, while multifunctional systems go a step further by incorporating targeting ligands, responsiveness to stimuli, or synergistic therapeutic modalities. Organometallic nanoconjugates are especially suited for such multifaceted functionality due to their structural versatility and capacity for fine molecular engineering [16]. Platinum (Pt)-based complexes have been conjugated with near-infrared (NIR) fluorescent dyes and encapsulated in mesoporous silica to achieve both fluorescence imaging and chemotherapeutic action. These constructs not only improve the pharmacokinetics of Pt drugs, but also allow imaging-guided delivery. Similarly, gold nanoparticles conjugated with doxorubicin and coated with pH-sensitive polymers have been developed for simultaneous photoacoustic imaging and pH-triggered drug release in acidic tumor environments [136].

A notable example is the design of ruthenium(II)-polypyridyl complexes incorporated into micelle-like structures with photodynamic and imaging properties. Upon

light activation, the complex generates reactive oxygen species (ROS) for effective tumor ablation while enabling fluorescence imaging of tumor margins. This dual capability significantly enhances therapeutic efficacy and minimizes damage to healthy tissues [137]. Multifunctional nanoconjugates may carry multiple drugs (e.g., chemotherapeutics and immunomodulators), offering synergistic effects in complex tumor microenvironments. Due to their intrinsic MRI contrast properties, iron oxide nanoparticles can be conjugated with anti-PD-L1 antibodies and loaded with siRNA to simultaneously visualize tumor sites and modulate immune checkpoints [138,139]. These dual- and multifunctional organometallic systems exemplify progress in nanoscale engineering, offering integrative platforms for enhanced diagnostics, targeted therapy, and precision medicine applications.

Real-time monitoring of therapeutic response

One of the most transformative advantages of theranostic nanoconjugates is their ability to monitor therapeutic responses in real time. Organometallic nanoconjugates, especially those with intrinsic imaging capabilities, such as magnetic, optical, or radioactive properties, allow dynamic visualization of nanoparticle biodistribution, drug release, tumor-targeting efficiency, and treatment efficacy [140]. Real-time monitoring aids in tailoring treatment regimens to the evolving tumor profiles of patients. Iron oxide nanoparticles are widely used as MRI contrast agents. When functionalized with therapeutic payloads such as doxorubicin or paclitaxel and conjugated with tumor-specific ligands, they provide not only high-resolution imaging, but also a quantitative assessment of drug accumulation in tumors [141]. A compelling example is the gadolinium-labelled gold nanostars employed in MRI-guided photothermal therapy. The system allowed continuous tracking of nanoparticle accumulation in tumor tissue and NIR-triggered heat generation for therapy. This integration has enabled personalized dosing schedules and improved therapeutic outcomes [142]. Another notable development is the creation of PET-active organometallic nanoconjugates using copper-64 or zirconium-89, which permit whole-body imaging of nanoparticle trafficking and pharmacokinetics. For instance, Cu-64-labeled platinum nanocages loaded with cisplatin have been used to monitor tumor uptake and drug release kinetics in vivo, leading to refined treatment planning [143]. Fluorescence and photoacoustic imaging modalities also support real-time evaluation at the cellular and tissue levels. Stimuli-responsive probes (e.g., redox-activated or enzyme-cleavable fluorophores) can be used when the drug is released inside tumor cells, offering high specificity and spatiotemporal resolution [144].

Future Perspectives and Opportunities

The field of organometallic nanoconjugates in biomedical imaging and theranostics is undergoing rapid evolution driven by advances in materials science, molecular biology, and precision medicine. Future directions in this interdisciplinary domain are expected to focus heavily on enhancing the precision, specificity, and responsiveness of nanosystems through next-generation molecular engineering. One of the most promising trends is the development of smart organometallic nanoconjugates that respond dynamically to biological environments. These “intelligent” platforms can integrate multiple stimuli-responsive elements such as pH, redox potential, temperature, enzymes, and light, allowing for controlled activation, targeted release, and simultaneous imaging feedback. For instance, nanoconjugates designed to activate photothermal or chemotherapeutic payloads only in the acidic tumor microenvironment or in the presence of specific overexpressed enzymes can significantly enhance selectivity and reduce off-target toxicity. Another emerging area of research is the development of personalized theranostic systems tailored to individual patient profiles. This includes the incorporation of patient-derived biomarkers, tumor-specific antigens, and real-time disease monitoring capabilities into the design of organometallic

nanoconjugates. By leveraging high-throughput screening data, genomics, and proteomics, future nanoconjugates can be optimized to enhance compatibility with a patient's molecular signature, enabling truly personalized medicine. Molecularly targeted imaging agents coupled with AI-driven diagnostic algorithms are likely to play a pivotal role in early cancer detection, therapy planning, and prognosis. The integration of biosensing technologies will also enhance the feedback loop between diagnosis and therapy. Organometallic nanoconjugates can be conjugated with biosensors for the real-time tracking of therapeutic efficacy, drug release profiles, and biological responses, enabling adaptive therapeutic strategies.

Multimodal and multifunctional platforms are expected to dominate theranostic research in the future. The ability of organometallic nanoconjugates to incorporate multiple imaging modalities, such as MRI, CT, PET, and optical imaging, into a single nanoplatform allows clinicians to harness complementary strengths, high spatial resolution, deep tissue penetration, and molecular specificity, thereby improving diagnostic accuracy. On the therapeutic front, combinations of photothermal therapy (PTT), photodynamic therapy (PDT), chemotherapy, and immunotherapy can be seamlessly integrated into a hybrid system. Such synergistic approaches are likely to improve therapeutic outcomes, overcome drug resistance, and reduce the required dosages. AI and machine learning (ML) are projected to revolutionize the design, screening, and optimization of organometallic nanoconjugates. These tools can predict physicochemical properties, biodistribution, toxicity profiles, and target-binding efficiency, thereby accelerating preclinical development. With sufficient clinical data, ML models can also help personalize dosing regimens and predict patient responses. The challenge lies in the integration of diverse contrast-generating agents within a single nanoplatform without compromising their individual physicochemical stability or signal efficiency. Differences in the optimal particle size, surface chemistry, and physicochemical environment required for each modality often create conflicts that complicate the design. Additionally, achieving balanced biodistribution and pharmacokinetics is critical because the incorporation of multiple imaging agents may alter clearance pathways or increase off-target accumulation. Another key challenge is controlling the signal interference, where one modality's optical or magnetic properties may quench or obscure another. Finally, biocompatibility and regulatory considerations present further hurdles, as multimodal constructs with complex compositions may raise toxicity concerns and complicate translational development. Automation and robotic synthesis may support high-throughput fabrication of libraries of organometallic nanoconjugates, enabling the rapid identification of optimal formulations for various disease models. Several challenges must be addressed, such as long-term toxicity, clearance pathways, regulatory approval, and synthesis scalability. The biocompatibility of organometallic cores, especially that of heavy metals, remains a concern for clinical translation. Addressing these concerns using novel surface coatings, biodegradable carriers, or excretable nanostructures is essential. Additionally, interdisciplinary collaboration among chemists, biologists, engineers, and clinicians will be critical in translating laboratory breakthroughs into clinical reality. The future of organometallic nanoconjugates in theranostics is bright and brimming with possibilities. Through continued innovations in molecular design, real-time imaging, and AI integration, these multifunctional platforms are poised to become central tools in the next generation of precision and personalized nanomedicine.

Conclusion

Organometallic nanoconjugates represent a rapidly evolving frontier in biomedical imaging and theranostics, bridging the disciplines of chemistry, nanotechnology, and medicine. Their unique structural versatility, tunable physicochemical properties, and

multifunctional capabilities enable precise molecular engineering for diagnostic and therapeutic applications. Over the past decade, significant efforts have been made to develop organometallic nanoconjugates incorporating metals, such as gold, ruthenium, platinum, and iron, which offer enhanced imaging contrast, targeted drug delivery, and effective therapeutic action, including photothermal, photodynamic, and chemotherapeutic effects. The integration of targeting ligands, stimuli-responsive elements, and multimodal imaging features has further enhanced the specificity and efficacy of these nanoconstructs, paving the way for personalized precision medicine. Importantly, the dual-role functionality of these systems in theranostics allows for the real-time monitoring of disease progression and therapeutic response, offering clinicians more control and flexibility in treatment regimens. Advances and challenges such as long-term toxicity, biocompatibility, large-scale synthesis, and regulatory approval still need to be addressed. Interdisciplinary efforts focusing on smart design, biosafety, and integration with digital tools such as AI and biosensors are likely to revolutionize the future landscape of organometallic theranostics. The main contributors to the long-term toxicity of organometallic nanoconjugates include the reactivity of metal centres, leading to ROS generation or unintended biomolecule binding, poor biodegradation of metallic cores causing tissue accumulation, and surface charge–induced immune activation. Uncontrolled metal ion release may result in oxidative stress, DNA damage, or organ-specific toxicity. Strategies such as polymer coatings, biodegradable or stimuli-responsive linkers, and stable ligand engineering have been employed to mitigate these issues. Designing ultrasmall or renal-clearable nanoconjugates and incorporating targeting ligands further enhance biocompatibility and reduce systemic exposure, collectively improving their translational safety. Organometallic nanoconjugates hold immense promise as transformative agents in modern medicine, offering new paradigms for diagnosis and treatment with molecular precision, real-time feedback, and multifunctionality. Continued innovation and translational research in this field are crucial for realizing their full potential in clinical applications.

Acknowledgments Q6

Conflict of Interest

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