

Recent Advances in Inorganic Chemistry: Metal-Based Therapeutics, Functional Materials, and Biomedical Applications

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Abstract:

Inorganic chemistry continues to supply a distinctive and expanding toolkit for biomedical application, exploiting coordination geometry, redox activity, and nanoscale physical properties that are largely inaccessible to purely organic small molecules. This review surveys four convergent domains of contemporary biomedical inorganic chemistry. We first examine metal-based therapeutics, tracing the field's foundation in platinum coordination chemistry through to non-platinum complexes and the covalent-binding design principles that inform rational metallodrug optimisation. We then survey metal–organic frameworks (MOFs), porous, tunable coordination materials increasingly applied across drug delivery, biosensing, and regenerative medicine. We further examine diagnostic and imaging applications, spanning magnetic resonance imaging contrast agents and the coordination chemistry underlying modern radiopharmaceutical design, before surveying inorganic nanomaterials — noble metal and metal oxide nanoparticles, lipid nanoparticle delivery systems, and their green-synthesised variants — and the biosensor platforms built upon them for point-of-care diagnostic application. We then examine the growing integration of computational and artificial intelligence-guided methodology, together with established rational drug design principles including fragment-based design, bioisosterism, and covalent inhibitor engineering, into inorganic and metal-based drug discovery, and survey sustainable synthetic methodology increasingly applied to functional materials synthesis more broadly. Finally, we critically examine the translational challenges — including nanomaterial characterisation burden, biodistribution uncertainty, and the persistent gap between preclinical materials characterisation and clinical application — that continue to constrain this mechanistically diverse field, and outline priority directions for continued development. We conclude that biomedical inorganic chemistry, spanning metal complexes, functional coordination materials, and inorganic nanomaterials, represents a mechanistically distinct and continually expanding complement to organic small-molecule and biologic therapeutics.

Keywords: Inorganic chemistry; metal complexes; metal–organic frameworks; coordination chemistry; nanomaterials; MRI contrast agents; radiopharmaceuticals; biosensors; functional materials; biomedical applications

Received: Jan. 14, 2026

Revised: Feb. 28, 2026

Accepted: March 28, 2026

Published: April 12, 2026

DOI: <https://doi.org/10.64474/3107-6386.Vol2.Issue1.6>

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1. Introduction

Inorganic chemistry occupies a distinctive position within the broader biomedical materials landscape, exploiting coordination geometry, variable oxidation states, redox activity, and nanoscale optical and magnetic properties that are largely inaccessible to purely carbon-based organic molecules. This mechanistic distinctiveness has motivated sustained biomedical application of metals and inorganic materials across a global disease burden that includes an estimated 19.3 million new cancer cases and almost 10 million cancer deaths across 36 cancer types in 2020 alone, alongside the diagnostic imaging, antimicrobial, and regenerative medicine applications surveyed throughout this review⁴⁰.

The modern era of biomedical inorganic chemistry is conventionally dated to Barnett Rosenberg's 1965 serendipitous discovery that platinum electrodes generated a compound capable of inhibiting bacterial cell division, an observation that led directly to cisplatin's development and established coordination chemistry as a legitimate, clinically productive branch of medicinal chemistry alongside organic small-molecule drug design. In the six decades since, this platinum foundation has expanded to a broader portfolio of clinically used metal-based agents, including silver sulfadiazine as a topical antibacterial, auranofin as an antirheumatic and repurposed anticancer/antimicrobial agent, and manganese-based contrast agents for magnetic resonance imaging, alongside an actively investigated pipeline of ruthenium-, gallium-, and iron-based anticancer complexes⁶. This review surveys four convergent domains of this expanding field: metal-based therapeutics (Section 2), metal-organic frameworks as functional biomedical materials (Section 3), diagnostic and imaging applications (Section 4), and inorganic nanomaterials and associated biosensor platforms (Section 5), before examining the growing role of computational and rational design methodology (Section 6), sustainable synthetic approaches (Section 7), and the translational challenges constraining this mechanistically diverse field (Section 8).

A unifying conceptual thread across these domains, developed throughout this review, is polypharmacology: many of the metal complexes, nanomaterials, and functional coordination materials surveyed here act through multiple, simultaneously engaged mechanisms rather than the single-target occupancy model that has historically dominated organic small-molecule drug design, a pattern consistent with the broader network pharmacology principle that complex diseases are often more durably addressed through coordinated multi-target intervention than through maximally selective single-target agents¹⁹.

A second unifying theme, distinct from but complementary to this polypharmacology principle, concerns the physical diversity of the materials surveyed in this review relative to the comparatively narrow structural vocabulary of organic medicinal chemistry. Where organic drug design operates principally through variation of covalent connectivity among a limited palette of common heteroatoms, inorganic and coordination chemistry can additionally vary metal identity, oxidation state, coordination number, and geometry, and, at the nanomaterial and framework scale, particle size, shape, porosity, and crystallinity, each of which

independently modulates biological activity. This substantially larger design space is simultaneously the field's greatest opportunity and its greatest translational complication, a tension that recurs throughout the domain-specific sections that follow and is addressed directly in Section 8.

2. Metal-Based Therapeutics

Following cisplatin's clinical establishment, complexes incorporating ruthenium, gold, copper, and palladium have been developed as alternatives offering improved selectivity, reduced cross-resistance, and mechanisms of action distinct from platinum-centred DNA binding. Preliminary evaluation of a novel palladium(II) complex against tongue squamous cell carcinoma cell lines demonstrated anti-proliferative activity, building on prior work characterising silver complexes against squamous cell carcinoma models specifically, illustrating a systematic, site-directed medicinal inorganic chemistry programme targeting this malignancy⁷.

A design principle increasingly applied to non-platinum metal complex optimisation is covalent, mechanism-based binding, in which a complex is engineered to form an irreversible or slowly reversible bond with a specific nucleophilic target residue rather than relying solely on non-covalent coordination interactions. This design logic parallels the resurgence of rationally designed covalent organic drugs over the past two decades, enabled by improved understanding of warhead reactivity–selectivity relationships and quantified through kinetic parameters describing the rate and equilibrium of bond formation¹⁷, and finds a direct precedent in the clinical translation of covalent KRAS(G12C) inhibitors developed against a target long considered undruggable using classical reversible approaches, together with the systematic mechanistic taxonomy developed to classify such covalent binding modes^{27,28}.

Structure–activity relationship considerations for metal complexes differ in important respects from those governing purely organic small molecules: coordination geometry, the identity and lability of coordinated ligands, and the metal's accessible oxidation states jointly determine a complex's reactivity, cellular uptake, and ultimate mechanism of action, such that comparatively modest changes in ligand identity can shift a complex's predominant activity from DNA-binding to enzyme-inhibitory or redox-cycling behaviour. This design flexibility enables mechanistic diversification unavailable to organic scaffolds constrained to a single, fixed binding mode, but it also means that structure–activity trends established for one metal or ligand class often generalise poorly to structurally related complexes of a different metal, complicating systematic, cross-complex optimisation relative to the comparatively more transferable structure–activity trends typically observed within a single organic heterocyclic scaffold family.

3. Metal–Organic Frameworks as Functional Biomedical Materials

Metal–organic frameworks (MOFs) — porous, crystalline materials assembled from metal ions or clusters bridged by organic ligands — have emerged as a structurally distinct class of biomedical inorganic material, exploiting high surface area, tunable pore size, and modular chemical functionality to enable applications spanning drug delivery, biosensing, bioimaging, and tissue engineering that are unavailable to discrete molecular metal complexes. A comprehensive review of MOF applications in regenerative medicine documents their particular promise in bone tissue engineering, exploiting their capacity for both osteoinductive and osteoconductive activity alongside integrated drug delivery function within theranostic scaffold designs¹, while a broader review of MOF biomedical applications catalogues drug delivery, cancer therapy, bioimaging, and wound healing as the principal current application areas, alongside critical discussion of MOF toxicity arising from reactive oxygen species generation and mitigation strategies through surface modification and green chemistry approaches².

The functionalisation flexibility that distinguishes MOFs from denser inorganic nanomaterials has been specifically highlighted as enabling target delivery and stimuli-responsive release behaviour, positioning functionalised MOFs as a versatile platform for bio-detection and disease therapy applications spanning multiple organ systems and disease areas³. This structural tunability directly parallels the intelligent, stimuli-responsive design logic increasingly applied across organic drug delivery systems more broadly, suggesting that MOF-based and organic polymeric delivery platforms are converging toward a shared design philosophy even as they remain materially distinct.

Figure 1. Convergent domains of modern inorganic chemistry in biomedical application

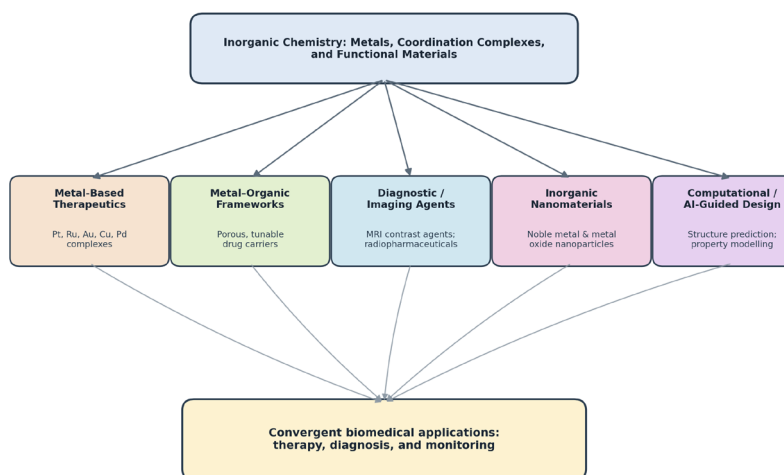


Figure 1. Convergent domains of modern inorganic chemistry in biomedical application, spanning metal-based therapeutics, metal–organic frameworks, diagnostic/imaging agents, inorganic nanomaterials, and computational design.

Table 1. Principal classes of biomedical inorganic materials surveyed in this review

Material class	Representative examples	Primary biomedical application	Ref.
Platinum/non-platinum metal complexes	Cisplatin; Ru, Au, Cu, Pd complexes	Anticancer chemotherapy; antimicrobial/antirheumatic repurposing	6,7
Metal-organic frameworks (MOFs)	Zn-, Fe-, Zr-based frameworks	Drug delivery; bioimaging; tissue engineering; biosensing	1,2,3
MRI contrast agents	Gadolinium(III) chelates; Mn-based agents	Diagnostic magnetic resonance imaging	4
Radiopharmaceuticals	Radiometal-chelate complexes	Targeted radionuclide imaging and therapy	5,6
Noble metal/metal oxide nanoparticles	Au, Ag, ZnO, TiO ₂ , Fe ₃ O ₄ nanoparticles	Photothermal/photodynamic therapy; ROS-mediated cytotoxicity; imaging	8,9,14

4. Diagnostic and Imaging Applications

Magnetic resonance imaging (MRI) contrast agents represent one of the most clinically established diagnostic applications of coordination chemistry, with tens of millions of contrast-enhanced MRI examinations performed annually worldwide using small, hydrophilic gadolinium(III)-based chelates. A comprehensive review of MRI contrast agent chemistry documents both the mechanism of action and long-term safety considerations underlying these clinically approved agents, and surveys the ongoing development of molecularly targeted and environmentally activatable next-generation contrast agents designed to sense pathological changes directly rather than providing purely non-specific contrast enhancement⁴.

Radiopharmaceutical development represents a closely related but chemically distinct diagnostic and therapeutic application of coordination chemistry, requiring precise characterisation of radiometal coordination behaviour to ensure stable, selective in vivo radionuclide delivery. Comprehensive characterisation of radionuclide coordination chemistry, employing electron paramagnetic resonance spectroscopy and complementary spectroscopic and computational methods, underpins the rational design of chelating ligands capable of stably sequestering therapeutic and diagnostic radiometals throughout their biological residence time⁵. A recent review specifically addressing radiopharmaceutical and boron neutron capture therapy coordination chemistry documents the clinical translation of targeted radionuclide therapies, including lutetium-177-labelled somatostatin and prostate-specific membrane antigen-targeted agents, and highlights the emerging integration of artificial intelligence into radiopharmaceutical and boron-agent design optimisation, a computational convergence discussed further in Section 6⁶.

5. Inorganic Nanomaterials and Biosensor Platforms

Beyond discrete molecular complexes and porous framework materials, inorganic nanoparticles constitute a further biomedical materials class exploiting nanoscale physical properties. Gold nanoparticles exhibit tunable plasmonic light absorption providing the physical basis for photothermal cancer therapy, converting absorbed near-infrared light into localised hyperthermic cytotoxicity⁸, while green-synthesised metal oxide nanoparticles offer improved biocompatibility for drug delivery application through plant-extract, microbial, and biopolymer-mediated synthesis routes, and green, biologically mediated synthesis has similarly been applied to silver nanoparticles evaluated for combined antimicrobial and cytotoxic activity^{9,14}.

Lipid nanoparticles (LNPs), though organic in their principal structural components, are frequently formulated with inorganic or metal-containing functional additives and are discussed here for their close mechanistic and translational relationship to the nanomaterial platforms surveyed throughout this section. LNPs self-assemble from an ionisable lipid component alongside helper phospholipids, cholesterol, and a polyethylene-glycol-conjugated lipid, with composition-dependent tuning of tissue tropism and endosomal escape efficiency governing therapeutic performance^{12,13}. The broader validation of nanoparticle-based medicine delivery, with a defined set of platforms having achieved regulatory approval across multiple oncology applications, and the more general engineering design principles for precision nanoparticle drug delivery, provide an established translational precedent directly relevant to the inorganic and hybrid nanomaterial platforms surveyed in this review^{10,11}.

Nanoparticle-based drug delivery systems developed for oral squamous cell carcinoma application illustrate how these inorganic and hybrid nanomaterial platforms are being adapted to address delivery challenges specific to individual malignancies and anatomical sites, including salivary clearance and mucosal permeability constraints distinct from those confronting systemically administered nanomedicines³⁹.

Translating the molecular and nanomaterial insights discussed above into clinical practice increasingly depends on biosensor platforms capable of detecting relevant analytes rapidly and sensitively at the point of care. Surface-enhanced Raman scattering (SERS)-based biosensors have emerged as a particularly sensitive platform for nucleic-acid biomarker detection, exemplified by a gold nanohexagon array coupled with hybridisation chain reaction amplification for sensitive salivary microRNA detection, and a complementary SERS-based lateral flow assay enabling simultaneous detection of multiple circulating tumour DNA targets for point-of-care head and neck cancer diagnostics^{15,16}.

6. Computational and Rational Design Methodology

Rational design methodology developed across organic medicinal chemistry is increasingly being applied to metal complex and inorganic materials optimisation. Quantitative drug-

likeness criteria based on molecular weight, lipophilicity, and hydrogen-bonding capacity, together with the oral bioavailability criteria addressing rotatable bond count and polar surface area, provide a systematic framework for evaluating the pharmacokinetic feasibility of metal complex candidates, even though metal complexes frequently violate these criteria owing to their distinctive coordination geometry and size^{18,37}. Bioisosteric replacement principles, substituting a ligand functional group with another of similar size, shape, or electronic character while preserving essential coordination geometry, offer a further transferable optimisation tactic for addressing metabolic liabilities or improving selectivity in metal complex design³⁸.

Fragment-based drug design, beginning from low-molecular-weight chemical fragments rather than drug-sized compounds, offers a further design paradigm directly transferable to metal complex and coordination material optimisation, particularly for targets lacking well-defined, readily druggable binding pockets. A two-decade retrospective on fragment-based drug discovery's impact, and a comprehensive account of the field's evolution from its origins through to contemporary integration with cryo-electron microscopy and computational fragment growth prediction, together provide the methodological foundation for extending this approach to inorganic and metal-containing chemical matter^{34,35}.

Artificial intelligence and machine learning methods are increasingly integrated across this computational design pipeline. High-accuracy structure prediction tools such as AlphaFold 3, capable of predicting protein–ligand and protein–metal complex structures with accuracy approaching experimental determination, substantially expand the range of metalloprotein and metal-binding targets amenable to structure-based design²⁰, while artificial intelligence methods developed for natural product drug discovery, spanning genome mining, activity prediction, and generative molecular design, offer directly transferable methodology for inorganic and metal-complex-inspired chemical matter, including a generative-AI-discovered candidate that has already progressed to randomised clinical trial evaluation for an unrelated indication^{21,29}.

Machine learning-based absorption-distribution-metabolism-excretion-toxicity (ADMET) property prediction, including systematic denoising of historical training data and broader analysis of the methodological elements underlying reliable molecular property prediction, is directly relevant to metal complex and nanomaterial candidate prioritisation, given the distinctive pharmacokinetic behaviour that metal-containing compounds frequently exhibit relative to purely organic chemical matter^{30,31}. Automated AI/ML virtual screening infrastructure designed to lower the infrastructural barrier to computational drug discovery, and therapeutic-area-adapted quantitative structure–activity relationship modelling approaches, provide a further template for extending rational, computationally guided inorganic materials design beyond well-resourced research centres^{32,33}. Finally, proteolysis-targeting chimeras (PROTACs), heterobifunctional molecules inducing targeted protein degradation rather than occupancy-based inhibition, represent an emerging design paradigm increasingly explored in

Interconnected Journal of Chemistry and Pharmaceutical Sciences (IJCPs)

ISSN: 3107-6386 | Vol. 02, Issue 01, Jan-April, 2026 | pp. 72-85

combination with metal-complex-based E3 ligase recruitment strategies, extending targeted protein degradation technology into the coordination chemistry space³⁶.

Table 2. Rational and computational design methodologies applied to inorganic and metal-based chemical matter

Methodology	Original organic chemistry context	Application to inorganic/metal chemistry	Ref.
Drug-likeness criteria	Lipinski Ro5; Veber oral bioavailability rules	Pharmacokinetic feasibility screening despite frequent violation by metal complexes	18,37
Bioisosteric replacement	Functional group substitution preserving pharmacophore	Ligand substitution preserving coordination geometry	38
Fragment-based design	Low-MW fragment screening and elaboration	Metal-binding fragment identification for challenging targets	34,35
AI structure prediction	AlphaFold protein structure prediction	Metalloprotein/metal-binding target structure prediction	20
Generative AI design	De novo organic candidate generation	Metal-complex-inspired chemical matter generation	21,29
PROTAC/targeted degradation	Heterobifunctional degrader molecules	Metal-complex-based E3 ligase recruitment strategies	36

Figure 2. Timeline of key milestones in biomedical inorganic chemistry

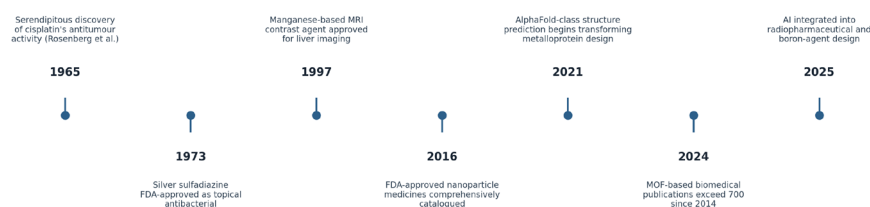


Figure 2. Timeline of key milestones in biomedical inorganic chemistry.

7. Sustainable Synthetic Methodology for Functional Materials

The synthesis of both the discrete metal complexes discussed in Section 2 and the nanomaterial platforms discussed in Section 5 has increasingly incorporated green and sustainable methodology, paralleling the broader shift toward atom-economical, catalytic synthesis across organic chemistry. Modern reaction classes — photoredox catalysis, electrochemistry, and carbon–hydrogen bond activation — have been successfully translated from milligram-scale laboratory demonstration to multi-hundred-gram and kilogram-scale production relevant to functional materials manufacture²⁴, with dual photoredox/nickel catalytic systems specifically

enabling mild-condition carbon–carbon and carbon–heteroatom bond formation applicable to ligand synthesis for the coordination complexes discussed throughout this review²⁵.

Metal-free and transition-metal-free coupling methodology, motivated by concerns over the cost, toxicity, and limited natural abundance of catalytic metals, offers a further green synthetic strategy directly relevant to ligand and functional material synthesis, exemplified by hypervalent-iodine-mediated coupling strategies that achieve high functional group tolerance while avoiding rare-metal catalysts²⁶. Click and bioorthogonal chemistry — modular, high-yielding, stereospecific reactions proceeding under mild conditions — have similarly been applied to metal complex bioconjugation and functionalisation applications, building on the foundational reliability criteria established for these reaction classes and their subsequent extension to physiological, catalyst-free conditions suitable for biomolecule and metal-complex modification alike^{22,23}.

8. Translational Challenges and Future Directions

Despite the mechanistic diversity and substantial preclinical evidence base surveyed across Sections 2 through 7, biomedical inorganic chemistry faces translational challenges that in several respects exceed those confronting purely organic small-molecule candidates, including nanomaterial and MOF characterisation burden, long-term biodistribution and clearance uncertainty for materials that may not be readily biodegraded, and regulatory frameworks that remain oriented around classical single-agent small-molecule paradigms rather than the multi-component, often polydisperse materials surveyed throughout this review.

Table 3. Principal challenges constraining clinical translation of biomedical inorganic chemistry

Challenge	Description	Illustrative consequence
Materials characterisation burden	Size, shape, surface chemistry, and porosity all influence biological activity of nanomaterials and MOFs	Higher development cost and batch-to-batch reproducibility burden than discrete small molecules
Long-term biodistribution uncertainty	Inorganic nanomaterials and MOFs may not be readily biodegraded or cleared	Uncertain chronic toxicity risk, particularly with repeat dosing
Metal complex SAR transferability	Structure–activity trends established for one metal/ligand class generalise poorly across metals	Complicates systematic, cross-complex rational optimisation
Computational method validation gap	AI/ML models trained predominantly on organic chemical space may generalise poorly to metal-containing compounds	Reduced reliability of computational predictions for inorganic and coordination chemistry candidates
Regulatory framework immaturity	Frameworks remain oriented around single-agent small-molecule paradigms	Novel MOF, nanomaterial, or combination metal-organic products face less well-defined regulatory pathways

Challenge	Description	Illustrative consequence
Preclinical-to-clinical evidence gap	Most inorganic materials candidates remain confined to in vitro or early in vivo evaluation	Few agents beyond established platinum chemotherapy and approved contrast agents reach registered clinical trials

Addressing these challenges will require standardised materials characterisation and reporting practices, dedicated long-term biodistribution studies, expanded computational training datasets specifically representing inorganic and metal-containing chemical space, and closer engagement between inorganic chemists and regulatory agencies to establish clearer translational pathways for the multi-component materials that increasingly characterise this field. Continued integration of the rational design, green synthesis, and computational methodologies surveyed in Sections 6 and 7 with the therapeutic, diagnostic, and materials applications surveyed in Sections 2 through 5 represents the most promising route toward narrowing this persistent translational gap.

9. Conclusion

Inorganic chemistry continues to supply a mechanistically distinctive and continually expanding toolkit for biomedical application, spanning metal-based therapeutics, metal-organic frameworks, diagnostic and imaging agents, and inorganic nanomaterials. These domains exploit coordination geometry, redox activity, and nanoscale physical properties that are largely unavailable to purely organic small molecules, offering complementary rather than competing capability relative to the organic small-molecule and biologic therapeutics that dominate contemporary pharmaceutical development. The growing integration of rational design methodology, computational and artificial intelligence-guided optimisation, and sustainable synthetic chemistry into this traditionally more empirical field is progressively transforming biomedical inorganic chemistry from a largely serendipitous discovery process toward a more systematic, structure- and mechanism-guided discipline. Nonetheless, materials characterisation burden, biodistribution uncertainty, and a persistent preclinical-to-clinical evidence gap continue to constrain translation of this technically sophisticated and mechanistically diverse literature. Continued progress will depend on treating metal-based therapeutics, functional coordination materials, and inorganic nanomaterials not as a peripheral complement to organic medicinal chemistry, but as an integral, mechanistically distinctive component of the broader biomedical chemistry toolkit, warranting continued rigorous mechanistic and translational investigation.

Six decades after cisplatin's serendipitous discovery first established coordination chemistry as a clinically productive medicinal discipline, the field surveyed in this review has grown to encompass functional materials, diagnostic agents, and computationally guided design methodology that Rosenberg's original bacterial growth experiments could scarcely have anticipated. The continued vitality of biomedical inorganic chemistry rests on the same basic premise that motivated that original discovery: that the distinctive coordination and physical chemistry of metals offers genuine, mechanistically differentiated therapeutic and diagnostic

opportunity, provided the translational rigor now increasingly applied across this field continues to mature alongside its considerable and still-expanding synthetic and mechanistic sophistication.

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