REVIEW ARTICLE

Recent Advances in Stimuli-responsive Hybrid Natural, Synthetic, and Inorganic Biomaterial Platform Systems for Diverse Cancer Immunotherapy and Therapeutic Applications

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Abstract

Cancer immunotherapy is a breakthrough in modern oncology, which uses immune system to identify and kill tumor cells. However, clinical efficacy is still hindered by barriers such as immune evasion, insufficient tumor targeting, poor therapeutic efficacy, and systemic toxicity. Recent advances in stimuli-responsive hybrid biomaterial platform systems based on inorganic, synthetic, and natural materials have been promising for improved therapeutic applications and cancer immunotherapy. These smart biomaterials are designed to respond specifically to exterior stimuli such as light, temperature, magnetic fields, ultrasound, and to internal stimuli such as pH, redox potential, enzymes, hypoxia, and reactive oxygen species. This responsiveness allows controlled and localized drug release, reducing off-target effects and improving the efficacy of treatment. This responsiveness lowers off-target effects and promotes treatment efficacy by facilitating controlled and site-specific release of medicines. Natural biomaterials such as chitosan, collagen, gelatin, alginate, and hyaluronic acid have better biocompatibility, biodegradability, and immunomodulatory properties. Synthetic polymers such as polycaprolactone, polyethylene glycol, and poly(lactic-co-glycolic acid) confer structural stability, tunable mechanical properties, and extended drug release. Inorganic nanomaterials such as gold nanoparticles, mesoporous silica nanoparticles, iron oxide nanoparticles, and metal-organic frameworks were applied to enhance drug loading efficiency, photothermal conversion, imaging capability, and magnetic responsiveness. The incorporation of these materials into hybrid systems has enabled multifunctional nanoparticles, injectable hydrogels, biomimetic carriers, and theranostic platforms for combined chemotherapy, photothermal therapy, photodynamic therapy, gene therapy, and immune checkpoint blockade. Stimuli-responsive hybrid biomaterials in the tumor microenvironment dramatically increase antigen presentation, dendritic cell activation, T-cell-mediated immune responses, and immunogenic cell death. New technologies such as biomimetic engineering, multi-stimuli-responsive nanomedicine, and artificial intelligence-assisted biomaterial design further expedite the development of next-generation precision medicines. Despite challenges associated with biosafety, large-scale fabrication, and clinical translation, these advanced biomaterial platforms hold great promise to enhance outcomes in cancer treatment and further the field of personalized cancer immunotherapy.

Key words: Cancer immunotherapy, Controlled drug release, Hybrid nanoplatforms, Nanomedicine, Smart drug delivery systems, Stimuli-responsive biomaterials, Tumor microenvironment

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INTRODUCTION

Despite major progress in chemotherapy, radiotherapy, surgery, and targeted therapies, cancer remains a leading killer worldwide. Immunotherapy has emerged as a breakthrough technique due to its ability to produce long-term anticancer immune responses and immunological memory.[1] Immune checkpoint blockade, cancer vaccinations, chimeric antigen receptor T (CAR-T) cell therapy, and cytokine therapy have shown great therapeutic efficacy in several tumors.[2] Yet, the therapeutic efficacy is hampered by various difficulties, including high systemic toxicity, quick drug degradation, immune escape, and inadequate immune infiltration.[3] Stimuli-responsive biomaterials have attracted much research because of their ability to intelligently release medicinal chemicals under certain physiological or externally applied conditions.[4] These techniques reduce the damage to normal tissues and improve the spatiotemporal control over the drug release and improve stability, immune activation, tumor targeting, and multimodal therapy.

CLASSIFICATION OF STIMULI-RESPONSIVE HYBRID BIOMATERIALS

Stimuli-responsive hybrid biomaterials are smart drug delivery systems that can release therapeutic agents in a controlled manner at the tumor site in response to specific internal or external stimuli. Examples of internal stimuli include reactive oxygen species (ROS), pH, redox potential and enzymes . Examples of external stimuli include light, heat, magnetic fields and ultrasound . These biomaterials enhance the effectiveness of cancer immunotherapy, reduce side effects and improve drug targeting. Depending on the stimulus, hybrid biomaterials can be classified as pH-responsive, redox-responsive, ROS-responsive, thermo-responsive, photo-responsive, enzyme-responsive and ultrasound-responsive systems. Table 1 summarizes their major immunotherapeutic applications and classification [5,7,8,15].

HYBRID SYSTEMS BASED ON NATURAL BIOMATERIALS

Natural biomaterials have attracted significant attention in cancer immunotherapy owing to their excellent biocompatibility, biodegradability, low immunogenicity, and intrinsic biological functionality. These polymers serve as versatile carriers for the controlled delivery of immunotherapeutic agents while minimizing systemic toxicity and improving therapeutic efficacy Their ability to undergo chemical modification further enables the fabrication of multifunctional hybrid nanoplatforms with enhanced targeting and stimuli-responsive drug release .Among natural polymers, chitosan is one of the most extensively investigated owing to its cationic nature, mucoadhesive properties, and ability to enhance cellular uptake. Chitosan-based nanocarriers facilitate efficient antigen delivery to antigen-presenting cells (APCs), promote dendritic cell maturation, and stimulate robust T-cell-mediated immune responses . In addition, chitosan can be readily modified with ligands, peptides, and nanoparticles to improve tumor-specific targeting and immunotherapeutic performance.[5]

Hyaluronic acid (HA) is another promising natural polymer widely used in hybrid nanocarriers because of its strong affinity for CD44 receptors, which are overexpressed in many types of cancer cells. HA-mediated receptor-targeted delivery enhances cellular internalization, prolongs circulation time, and facilitates selective accumulation of therapeutic agents within the tumor microenvironment . Furthermore, HA-based systems can be engineered to respond to hyaluronidase enzymes, enabling controlled drug release specifically at tumor sites .Alginate hydrogels have emerged as attractive biomaterials for immunotherapy due to their excellent biocompatibility and three-dimensional network structure.

These hydrogels effectively encapsulate immune cells, cytokines, vaccines, and therapeutic proteins, providing sustained release and localized immune activation . Their injectable and stimuli-responsive properties further support tissue engineering applications and localized cancer immunotherapy .Similarly, gelatin-based nanoparticles possess excellent biodegradability and inherent cell-adhesive properties that facilitate efficient cellular uptake. Gelatin is susceptible to degradation by matrix metalloproteinases (MMPs), enabling enzyme-responsive drug release within tumor tissues. These nanoparticles have been shown to enhance antigen presentation, activate immune cells, and improve therapeutic efficacy while reducing off-target toxicity.[6]

Recent advances have focused on the development of hybrid systems that integrate natural polymers with inorganic nanomaterials to combine the advantages of both materials. These hybrid platforms exhibit enhanced structural stability, controlled drug loading, improved tumor targeting, and synergistic therapeutic functions.[7] For example, gold nanoparticles (AuNPs) coated with chitosan have demonstrated enhanced photothermal conversion efficiency, increased dendritic cell activation, and stronger cytotoxic T-cell responses when combined with photothermal therapy. Likewise, mesoporous silica nanoparticles (MSNs) functionalized with hyaluronic acid or conjugated with immune checkpoint inhibitors have shown improved tumor accumulation, sustained release of immunotherapeutic agents, and enhanced efficacy of immune checkpoint blockade therapy by promoting T-cell infiltration into tumors .Overall, hybrid systems based on natural biomaterials

Table 1: Types of stimuli-responsive hybrid biomaterial systems in cancer immunotherapy

Stimulus type	Hybrid components	Mechanism	Immunotherapeutic application
pH-responsive	Chitosan+PLGA+Gold nanoparticles	Release of drugs in an acidic tumor environment	Delivery of immune checkpoints
Redox-responsive	PEG+Disulfide bonds+Mesoporous silica	Release induced by glutathione	Delivery of antigens
ROS-responsive	Hyaluronic acid+Iron oxide	Cleavage of ROS	Polarization of macrophages
Thermo-responsive	PNIPAM+Magnetic nanoparticles	Drug release caused by heat	Immunotherapy for hyperthermia
Photo-responsive	Graphene oxide+Liposomes	Photothermal activation caused by light	Combined PDT/PTT immunotherapy
Enzyme-responsive	Gelatin+MMP-sensitive peptides	Degradation caused by enzymes	Release of antigens unique to tumors
Ultrasound-responsive	Lipid nanoparticles+Perfluorocarbon	Release mediated by cavitation	Increased immune infiltration

PLGA: Poly (lactic-co-glycolic acid), PEG: Polyethylene glycol, PNIPAM: Poly (N-isopropylacrylamide), ROS: Reactive oxygen species, PDT: Photodynamic therapy, PTT: Photothermal therapy, MMP: Matrix Metalloproteinases

Table 2: Representative hybrid biomaterial systems for cancer immunotherapy

Hybrid platform	Stimulus	Therapeutic cargo	Cancer model	Major outcome
Chitosan-gold nanoparticles	NIR light	PD-L1 inhibitor	Melanoma	Increased activation of T cells
PLGA-iron oxide nanoparticles	Magnetic field	Doxorubicin+CpG	Breast cancer	Enhanced polarization of macrophages
Hyaluronic acid-silica nanoparticles	Acidic pH	Anti-PD-1 antibody	Colon cancer	Better targeting of tumors
Gelatin-manganese oxide nanoparticles	ROS	Tumor antigen	Lung cancer	Improved immunological memory
Lipid-polymer hybrid nanoparticles	Heat	mRNA vaccine	Ovarian cancer	Enhanced presentation of antigens
Graphene oxide composites	Laser irradiation	Photosensitizer	Glioblastoma	Increased mortality of immunogenic cells

PLGA: Poly (lactic-co-glycolic acid), NIR: Near-infrared, ROS: Reactive oxygen species, mRNA: Messenger ribonucleic acid, PD-L1: Programmed death-ligand 1, PD-1: Programmed cell death protein 1a, CpG: Cytosine–phosphate–Guanine

represent a promising strategy for next-generation cancer immunotherapy. By integrating the biological advantages of natural polymers with the unique physicochemical properties of inorganic nanomaterials, these multifunctional platforms offer improved immune activation, targeted drug delivery, controlled release, and multimodal therapeutic capabilities, ultimately enhancing antitumor efficacy while minimizing systemic adverse effects.[8]

Natural polymers have drawn a lot of investigation due to their intrinsic biological usefulness, minimal toxicity, and biodegradability.[9] Nanocarriers based on chitosan show strong mucoadhesive properties and efficient delivery of antigen to antigen-presenting cells.[10] Hyaluronic acid is responsible for cellular internalization through CD44 receptors overexpressed in malignancies.[11] Alginate hydrogels have been extensively explored as a platform for targeted delivery of immunotherapeutics, due to their ability to encapsulate immune cells and cytokines.[12] Gelatin-based nanoparticles increase immune activation and enable enzyme-responsive degradation in tumor tissues.[13]

Recent hybrid systems of inorganic nanoparticles and natural polymers have substantially improved the therapeutic outcomes. For instance, gold nanoparticles coated with chitosan have exhibited enhanced photothermal effects and activation of dendritic cells.[14] Similarly, mesoporous silica nanoparticles modified with checkpoint inhibitors have been demonstrated to improve checkpoint inhibitor transport and tumor targeting [Figure 1 and Table 1].[15]

HYBRID SYSTEMS BASED ON SYNTHETIC POLYMERS

Synthetic polymers possess high structural flexibility and tunable drug release kinetics.[16] Polyethylene glycol (PEG), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and poly(N-isopropylacrylamide) (PNIPAM) are widely used in cancer immunotherapy.[17] PLGA nanoparticles increase circulation time and improve antigen stability.[18] The thermoresponsive PNIPAM devices can be

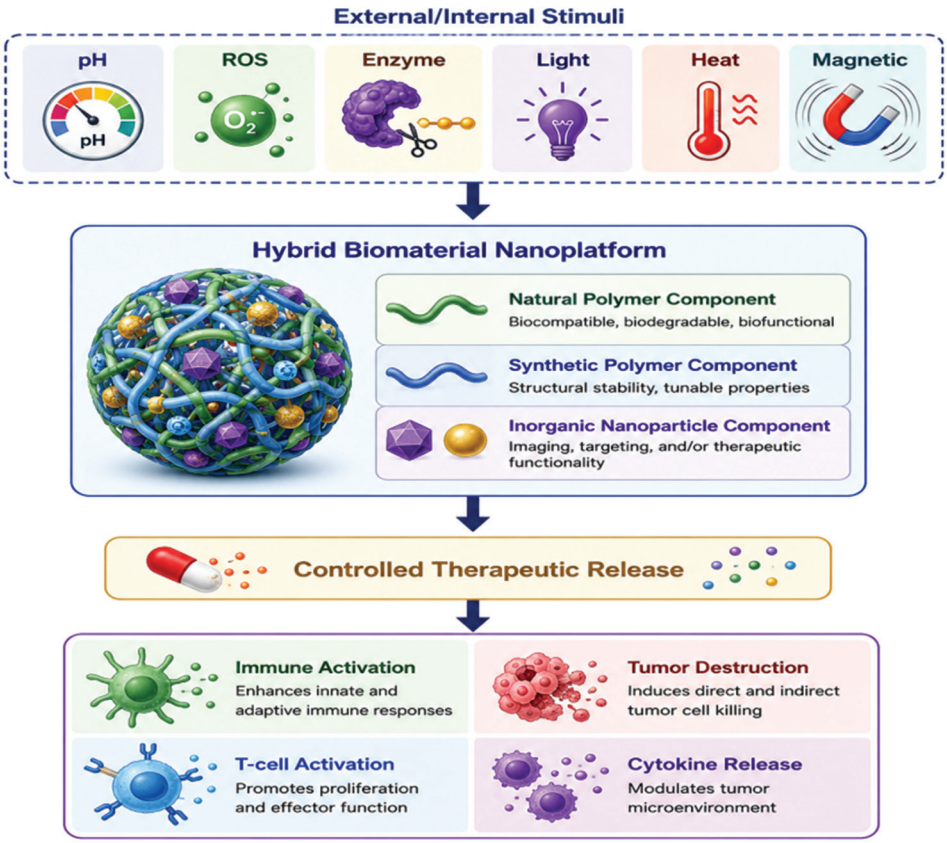

Figure 1: Architecture of stimuli-responsive hybrid biomaterial system

used for the thermally triggered release of immunotherapeutic medicines.[19] PEGylation increases the circulation time of nanoparticles and reduces opsonization.[20]

Recently, synthetic polymers have been mixed with inorganic nanoparticles to provide multimodal therapy. Enhanced macrophage reprogramming and magnetic targeting were observed using PLGA-coated iron oxide nanoparticles.[21] Synthetic polymer-lipid hybrid nanoparticles have also demonstrated better messenger ribonucleic acid (mRNA) vaccine delivery efficiency.[22]

CANCER IMMUNOTHERAPY USING INORGANIC NANOMATERIALS

Inorganic nanoparticles have unique optical, magnetic, electrical, and catalytic properties that can be utilized for cancer immunotherapy.[23] The gold nanoparticles exhibited good photothermal conversion efficiency and tumor antigen release enhancement after laser irradiation.[24] As a result, mesoporous silica nanoparticles have a high drug loading capacity and controlled release behavior.[25] Nanoparticles of iron oxide for magnetic resonance imaging and magnetic targeting.[26] Calcium phosphate nanoparticles as mimics of biological minerals for efficient delivery of vaccines and nucleic acids.[27]

Fluorescence imaging and diagnostics are enabled by quantum dots and up-conversion nanoparticles.[28] Hybrid inorganic-organic systems have emerged as powerful platforms that can combine treatment and diagnosis in a single nanostructure.[29]

SYSTEMS RESPONSIVE TO TUMOR MICROENVIRONMENT (TME)

The TME is characterized by acidic pH, elevated glutathione, hypoxia, and abnormal enzyme expression.[30] These problematic qualities are exploited by stimuli-responsive biomaterials to trigger tailored therapeutic release. pH-responsive nanoparticles for selective drug release in acidic tumor tissues.[31,32] Increased intracellular glutathione levels stimulate redox-sensitive systems with disulfide bonds.[33] Hypoxia-responsive nanocarriers for enhanced photodynamic therapy (PDT) and targeting of oxygen-deficient tumors.[34]

Reactive oxygen species (ROS) responsive systems enhance oxidative stress and induce immunogenic cell death.[35] These approaches promote cytotoxic T-cell infiltration and improve antigen presentation.[36]

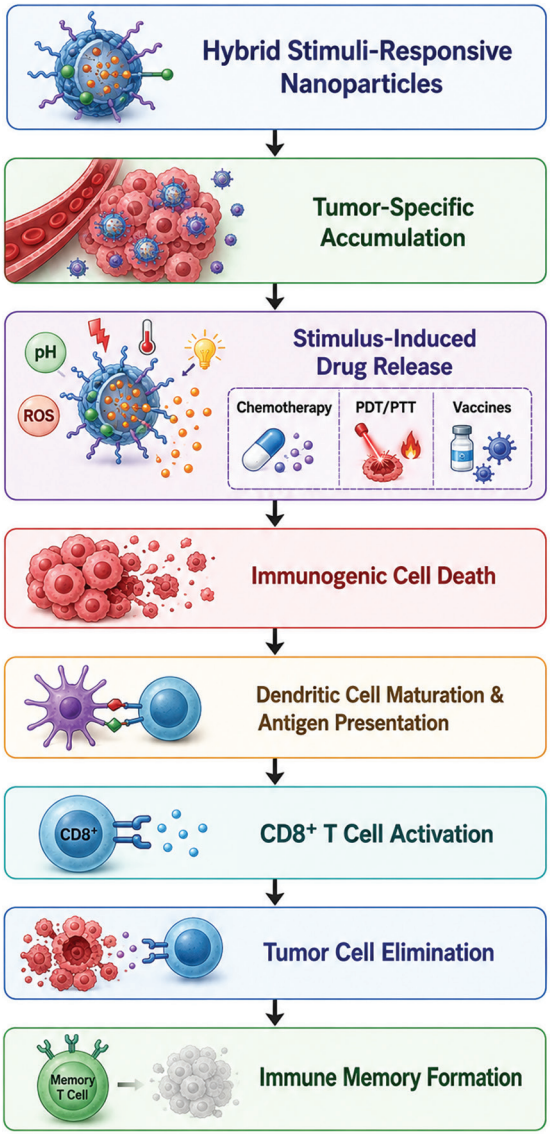

Figure 2: Mechanism of hybrid biomaterial-mediated cancer immunotherapy

IMMUNOTHERAPY PLATFORMS THAT ARE PHOTORESPONSIVE AND THERMOS RESPONSIVE

PTT and PDT have gained a lot of attention due to their capacity to promote immunogenic tumor cell death.[37] High photothermal conversion efficiency of black phosphorus nanosheets, graphene oxide, and gold nanorods.[38] The photo-responsive hybrid devices can realize the specific tumor ablation and immune activation under the near-infrared light.[39] Thermo-responsive polymers such as PNIPAM change phase at high temperatures, allowing for controlled medication delivery.[40]

The combination of PTT/PDT with immune checkpoint inhibition has shown great therapeutic efficacy in pre-clinical investigations.[41] Furthermore, photoactivated pathways increase T-cell activation and maturation of dendritic cells.[42]

METHODS OF COMBINATION THERAPY

Hybrid biomaterial systems are more and more used in combination with chemotherapy, radiation, gene therapy, and immune checkpoint inhibition.[43] The combination therapy promotes immune cell infiltration and presentation of tumor antigens.[44] Simultaneous delivery of immunological adjuvant and chemotherapeutic drugs on nanoplatforms promotes the synergistic therapeutic effect.[45] The combination of photothermal therapy with checkpoint inhibitors has shown significant tumor shrinkage and reduced metastasis.[46] mRNA-loaded lipid-polymer hybrid nanoparticles have emerged as promising platforms for cancer vaccination.[47] Biomaterial-assisted administration of CAR-T cells also improves tumor penetration and retention of immune cells.[48]

DRUG DELIVERY MECHANISMS AND RELEASE KINETICS

Drug delivery systems may improve the efficacy of cancer therapies by enhancing tumor targeting and minimizing systemic toxicity.[49] The targeting of tumors can be achieved mainly by the passive and active targeting processes. The passive targeting relies on the enhanced permeability and retention effect, which utilizes the leaky vasculature and poor lymphatic drainage in tumor tissues to promote the accumulation of the nanoparticles.[50] Active targeting is the modification of nanoparticle surface with ligands such as antibodies, peptides, folic acid, or hyaluronic acid to specifically interact with tumor cell receptors and improve cellular absorption.[51] Controlled release kinetics enable drug release in a sustained and site-specific manner by diffusion, degradation, or stimuli-responsive mechanisms such as pH, ROS, enzymes, or temperature changes in the TME.[52] These technologies minimize negative effects and early drug leakage while improving therapeutic efficacy.[53]

The main internalization pathway of nanoparticles by cells is by endocytosis, including caveolae-mediated endocytosis and clathrin-mediated endocytosis.[54] Intracellular trafficking of nanoparticles through endosomes and lysosomes after internalization can influence drug stability and therapeutic effectiveness.[55]

Endosomal escape is an important step in the intracellular delivery of proteins and nucleic acids.[56] Nanoparticles can utilize strategies including the proton sponge effect, membrane instability, and cell-penetrating peptides to escape from endosomes and deliver therapeutic cargo into the cytoplasm prior to lysosomal destruction.[57]

ADVANCED FABRICATION TECHNIQUES AND NANOTECHNOLOGY

Recent advances in nanotechnology have considerably contributed to the development of precision medicine platforms and cancer immunotherapy.[58] Nano formulations include liposomes, polymeric nanoparticles, dendrimers, and mesoporous silica nanoparticles. These formulations provide increased drug stability, targeted delivery, controlled release, and less systemic toxicity.[59] Nanotheranostic systems are also being developed for contemporaneous imaging and therapy for cancer cure.[60] Microfluidic technology has enabled the manufacture of highly homogenous nanoparticles with precise control over particle size, shape, and encapsulation efficiency.[61] Microfluidics has also been used for high-throughput screening of cancer treatments and the scale-up production of hybrid biomaterials.[62]

The expanding utilization of three-dimensional (3D) bioprinting for the development of biomimetic tumor models that faithfully mimic the original TME.[63] Hydrogels, cells, and growth hormone bioinks can be used to form complex tissue structures for drug screening and personalized cancer treatment.[64] Recently, the combination of 3D bioprinting with microfluidic and organ-on-a-chip technology has been pointed out to improve physiological relevance in cancer research.[65] Organ-on-chip devices are in vitro models of physiological processes at the organ level, integrating tissue engineering and microfluidics.[66] Tumor-on-chip systems are a powerful tool to evaluate the efficacy and safety of therapies as they may mimic vascular flow, immunological interactions, and tumor heterogeneity.[67] Such technologies are increasingly being applied in preclinical nanomedicine and personalized oncology [Figure 2 and Table 2].[68]

Recently, artificial intelligence (AI)-assisted biomaterial design has received a great deal of attention to accelerate biomaterial discovery and optimization.[69] Machine learning algorithms can anticipate drug release kinetics, biological interactions, nanoparticle behavior, and therapeutic effects, and so save development time and experimental costs.[70] In the future, AI-driven nano theranostics will be expected to play an important role in the precision treatment of cancer.[71]

CHALLENGES AND FUTURE PERSPECTIVES

Hybrid biomaterial systems have progressed significantly, but still face several challenges limiting their application in the clinic.[72] Complex synthesis procedures, challenges in large-scale production, low reproducibility, and long-term biosafety issues are still major hurdles.[73] Further investigations on immune-related side effects and varied tumor responses should likewise be warranted.[74] Future research should focus on customized biomaterial platforms, AI-aided nanomedicine design, degradable inorganic materials, and scalable manufacturing processes.[75]

The fusion of biomaterials with *CRISPR* gene editing, mRNA treatments, and advanced imaging technologies is projected to transform precision cancer immunotherapy.[76] The next generation of intelligent oncological treatments may be multi-functional hybrid systems capable of diagnosing, treating, and monitoring the immune system simultaneously.[77]

CONCLUSION

Stimuli-responsive hybrid biomaterials, which include inorganic, synthetic, and natural components, have appeared as effective tools for cancer immunotherapy. These advanced nanoplatforms provide superior immune activation, enhanced tumor targeting, controlled drug release, and accurate therapeutic administration. Recent advances have shown their great potential to overcome immunosuppressive TMEs and improve therapy outcomes. Further multidisciplinary research on materials science, nanotechnology, immunology, and clinical oncology will promote the development of safe and efficient personalized cancer therapies.

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