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How can metal-organic frameworks be rationally designed to modulate the tumor microenvironment and thereby inhibit multiple hallmarks of cancer?

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ABSTRACT

This Review examines three interconnected themes: the Hallmarks of Cancer, Metal-Organic Frameworks (MOFs), and MOF-based immunotherapy strategies. The Hallmarks of Cancer offer a conceptual framework for understanding tumor development, while MOFs have emerged as versatile platforms for biomedical applications. We outline the core principles of each area, highlighting the structural and functional properties of MOFs that enable targeted therapeutic use, and examine how MOF-integrated immunotherapy can modulate key cancer hallmarks. Finally, we unify these concepts into a single framework illustrating their interplay and relevance for next-generation cancer therapies.

This review article was drafted and formatted in Microsoft Word. The topic was chosen for both personal and scientific reasons: a family member's experience with prostate cancer, combined with the author's background as a chemistry Olympiad student and interest in the work of MOF researchers Susumu Kitagawa, Richard Robson, and Omar M. Yaghi. The manuscript follows a seven-section structure: Abstract, Introduction, Hallmarks, MOFs, Application, Conclusion, References. Literature was gathered from the following sources: Google Scholar, PubMed, general web search, and papers recommended by the professor with whom this article was written. Publication date ranges varied from 1998 to 2026, with most cancer-related papers spanning between 2007 and 2010, while MOF-related papers were more recent. General searching strategies normally started with reading the papers sent by the professor, and reading the other ones that were cited in the initial articles. The inclusion criteria prioritized peer-reviewed and more cited papers, with sufficient methodological detail. When it came to similar works about a specific topic, we usually followed our inclusion criteria, however, in some cases, two papers complemented each other, and both were chosen, e.g. Douglas Hanahan's 2011 and 2026 articles. Sources were reviewed qualitatively, with relevant findings synthesized into a coherent narrative and cited using a numbered system, with full details in the References section. Lastly, the section of hallmarks of cancer that was used in this paper, though based on several works of Douglas Hanahan, was mainly inspired by his 2026 work. The review focused on the nine core cancer hallmarks because they represent discrete, therapeutically targetable capabilities of tumor cells, whereas the additional dimensions introduced by Hanahan (2026), although biologically important, are broader contextual concepts beyond the therapeutic scope of this review.

INTRODUCTION

Cancer is a multifactorial and heterogeneous group of diseases characterized by the uncontrolled proliferation of abnormal cells, their ability to evade regulatory constraints, and, in many cases, their capacity to invade surrounding tissues and disseminate to distant organs. Tumor development is driven by a combination of genetic alterations, epigenetic reprogramming, and dynamic interactions with the surrounding microenvironment. These processes enable cancer cells to overcome physiological barriers that normally maintain tissue homeostasis (1).

To provide a unifying framework for understanding this complexity, the concept of the "hallmarks of cancer," introduced by Douglas Hanahan and Robert A. Weinberg, defines a set of acquired biological capabilities that govern tumor initiation, progression, and metastasis. Together with three other important conceptual dimensions, these hallmarks provide a systematic framework for identifying therapeutic vulnerabilities (2).

From a therapeutic perspective, each hallmark represents a potential point of intervention. However, despite significant advances in conventional treatments – including chemotherapy, radiotherapy, and targeted therapies – major challenges remain, particularly in achieving selective delivery, minimizing systemic toxicity, and overcoming resistance mechanisms. These limitations highlight the need for more precise and adaptable therapeutic strategies (2).

In this context, nanotechnology-based approaches have emerged as promising tools for improving treatment efficacy. Among these, MOFs have attracted increasing attention due to their unique structural and chemical properties. Composed of metal ions or clusters coordinated with organic ligands, MOFs exhibit high porosity, large surface area, and tunable functionality, enabling the encapsulation and controlled release of a wide range of therapeutic and diagnostic agents. Their modular design allows precise engineering of physicochemical properties, facilitating targeted delivery, stimuli-responsive release, and multifunctional platform development (3).

Importantly, the versatility of MOFs makes them particularly well suited for targeting the biological processes underlying cancer hallmarks.

Recent research has increasingly focused on leveraging MOFs to modulate key aspects of tumor biology. (4), (5), (6), (7), (8), (9).

In this article, we examine the fundamental principles of cancer biology and the hallmarks of cancer, followed by an overview of MOFs and their physicochemical characteristics. We then explore how these platforms can be strategically applied to target specific cancer hallmarks, with an emphasis on emerging approaches in tumor therapy. By integrating these domains, we aim to highlight the potential of MOFs as powerful tools in the development of next-generation cancer treatments.

Hallmarks of cancer:

Hallmark 1: Sustaining Proliferating Signaling

For a normal cell to initiate division, it requires external growth factors that activate tightly regulated signaling pathways controlling progression through the cell cycle. In contrast, cancer cells acquire the ability to sustain proliferative signaling, thereby bypassing dependence on physiological growth cues and becoming autonomous in their growth behavior. This capability is frequently driven by oncogenes that reprogram intracellular signaling networks to provide persistent mitogenic stimulation, among which KRAS is one of the most prominent, constitutively activating downstream pathways such as MAPK and PI3K-AKT through point mutations. Additionally, tumor cells may establish autocrine signaling loops by producing their own growth factors or exploit paracrine interactions with stromal cells to sustain proliferation (10). Despite this strong drive toward continuous signaling, excessively high oncogenic activity can activate intrinsic fail-safe mechanisms such as senescence or apoptosis, meaning that tumor cells often maintain a balance between sufficient proliferative stimulation and avoidance of anti-proliferative responses (11), (12), (13). In this context, targeting sustained proliferative signaling remains a major therapeutic challenge, particularly because key drivers such as KRAS have historically been difficult to inhibit directly (1).

Hallmark 2: Inactivating growth suppressors

Evading growth suppressors is a hallmark of cancer that closely complements sustained proliferative signaling. While oncogenes drive continuous cell division, cancer cells must simultaneously disable the regulatory systems that normally restrain proliferation and maintain tissue homeostasis. These growth-inhibitory mechanisms operate through both cell-intrinsic and cell-extrinsic pathways and are frequently inactivated or attenuated during tumor development. Central to this process are tumor suppressor genes, which encode proteins responsible for enforcing checkpoints throughout the cell cycle. Under normal conditions, progression through the cell cycle is controlled by cyclin-dependent kinases (CDKs), whose activity is tightly regulated by inhibitory proteins such as CDKN1A and CDKN1B. These inhibitors act as molecular “brakes,” halting the cell cycle in response to stress signals such as DNA damage, thereby allowing repair before division proceeds (2), (14).

At the core of these regulatory networks are two major tumor suppressors: the retinoblastoma protein (RB) and TP53. RB regulates cell division and prevents transition into the DNA synthesis phase unless proper growth signals are present (14), (15), (16), and cancer cells with defects in RB pathway function lack a critical gatekeeper of cell-cycle progression whose absence permits persistent cell proliferation (1). On the other hand, TP53 functions as a central sensor of cellular stress, responding to DNA damage, hypoxia, and oncogenic signaling by inducing cell-cycle arrest, senescence, or apoptosis. However, mutations in TP53 – among the most common alterations in cancer – disable these protective responses and, in some cases, confer additional tumor-promoting functions (2), (1).

Other regulatory systems further contribute to growth suppression. At the tissue level, mechanisms such as contact inhibition restrict cell proliferation when cells reach confluence. Additionally, the tumor microenvironment imposes constraints through limited oxygen and nutrient availability, conditions that normal cells cannot tolerate but cancer cells gradually adapt to (1). The TGF-beta signaling pathway provides another layer of control, initially acting as a potent inhibitor of proliferation, although it is often co-opted in advanced cancers to promote invasion and metastasis (17), (18), (19). Importantly, these tumor suppressor systems exhibit functional redundancy, meaning that multiple pathways typically need to be disrupted for a cell to fully escape growth control.

Hallmark 3: Resisting programmed cell death

A qualitatively distinct hallmark of cancer is the ability of tumor cells to evade programmed cell death, thereby bypassing a critical protective mechanism that normally eliminates damaged or abnormal cells. In healthy tissues, cells experiencing stress – such as DNA damage, oncogenic signaling, hypoxia, or nutrient deprivation – are removed through tightly regulated death pathways. Cancer cells, however, acquire the capacity to suppress or circumvent these processes, allowing survival under conditions that would otherwise be lethal. Among these mechanisms, apoptosis is the most extensively characterized and represents a primary barrier to tumor development. It is executed through two major pathways that converge on the activation of caspases, a family of proteases responsible for controlled cellular dismantling (2). The extrinsic pathway is initiated by extracellular ligands, such as Fas ligand, which bind to death receptors on the cell surface and trigger a proteolytic cascade leading to caspase activation (2), (1). In contrast, the intrinsic pathway is activated by intracellular stress signals and is regulated by the BCL-2 family, which controls mitochondrial membrane integrity (13). Central to these processes is TP53, which functions as a master regulator of cellular stress responses by inducing transcriptional programs that promote either cell-cycle arrest or apoptosis. Loss or mutation of TP53 simultaneously disrupts both growth control and apoptotic signaling, significantly enhancing cell survival. Cancer cells further evade apoptosis through upregulation of anti-apoptotic proteins, downregulation of pro-apoptotic factors, and activation of survival pathways such as those mediated by IGF signaling, collectively shifting the intracellular balance toward survival (2), (1), (20), (21).

In addition to apoptosis, alternative forms of programmed cell death, such as necroptosis, ferroptosis, pyroptosis, and regulated autophagy, contribute to tumor suppression, although cancer cells often develop resistance across multiple pathways. Necrosis, in contrast, is a process that can promote tumor progression by inducing inflammation and remodeling the tumor microenvironment. These overlapping and context-dependent death pathways highlight the complexity of cell death regulation in cancer and underscore the importance of survival mechanisms for tumor progression (1), (22), (23), (24), (25).

From a therapeutic perspective, overcoming resistance to cell death remains a central challenge. Strategies such as BH3 mimetics, which inhibit anti-apoptotic BCL-2 family proteins, aim to restore apoptotic signaling; for example, venetoclax has demonstrated clinical success in certain hematologic malignancies. However, limited efficacy in solid tumors and the emergence of resistance necessitate more advanced delivery and targeting approaches (2).

Hallmark 4: Establishing replicative immortality

A defining hallmark of cancer is the ability of tumor cells to achieve unlimited replicative potential, enabling the formation of macroscopic tumors. This property sharply contrasts with most normal somatic cells, which are inherently limited in the number of times they can divide due to two major barriers: replicative senescence, a stable growth arrest, and crisis, a state associated with extensive cell death. During repeated cycles of division, normal cells first enter senescence and, if this barrier is bypassed, eventually reach crisis. Only rare cells that overcome both barriers acquire the capacity for indefinite proliferation, a process referred to as immortalization and characteristic of most cancer cells (2), (1).

Central to this limitation is the progressive shortening of telomeres, repetitive DNA sequences located at the ends of chromosomes. Telomeres shorten with each cell division, eventually losing their protective function and being recognized as DNA damage. Critically shortened telomeres lead to chromosomal instability, ultimately triggering senescence or crisis. These barriers are reinforced by tumor suppressors such as TP53 and RB, which coordinate responses to telomere dysfunction and prevent uncontrolled proliferation (2).

To overcome these limitations, cancer cells must stabilize their telomeres. In most human tumors, this is achieved through activation of telomerase, a reverse transcriptase that elongates telomeric DNA. Its catalytic subunit, TERT, is typically repressed in normal somatic cells but becomes reactivated in cancer, allowing cells to maintain telomere length and evade both senescence and crisis. Importantly, telomere dysfunction plays a dual role in tumorigenesis: while it initially suppresses tumor growth by inducing senescence or apoptosis, continued proliferation in the absence of proper checkpoint control can promote genomic instability and accelerate oncogenic evolution (2), (1).

Hallmark 5: Inducing or accessing vasculature

The ability to induce angiogenesis represents a fundamental hallmark of cancer, reflecting the requirement of tumors to secure a sufficient supply of oxygen and nutrients while removing metabolic waste. In normal tissues, this exchange is maintained by a highly organized vascular network; however, in tumors, this becomes a limiting factor, as cells located more than ~100 μm from a capillary experience hypoxia and nutrient deprivation, often resulting in necrosis. Consequently, sustained tumor growth depends on the establishment of a functional blood supply. Beyond nutrient delivery, tumor-associated vasculature actively shapes tumor biology by secreting paracrine factors that influence cancer cell behavior, stromal interactions, and immune responses within the tumor microenvironment (2).

The transition from a non-angiogenic to an angiogenic state – known as the angiogenic switch – is a critical step in tumor progression and is regulated by a balance between pro- and anti-angiogenic signals (1), (26), (27). Tumor progression is typically associated with a shift toward pro-angiogenic signaling. Once activated, angiogenesis proceeds through endothelial cell proliferation, migration, and organization

into new vascular structures. In parallel, tumors may exploit vascular co-option, hijacking pre-existing vessels as an alternative strategy (1), (2).

Tumor vasculature is structurally and functionally abnormal, characterized by disorganized architecture, irregular vessel diameter, and high permeability. These abnormalities lead to inefficient perfusion, elevated interstitial pressure, and persistent hypoxia, which further stimulates angiogenic signaling and contributes to therapeutic resistance. Moreover, the disorganized vasculature can limit immune cell infiltration, reinforcing immune evasion. Angiogenesis is also strongly influenced by the tumor microenvironment, where non-malignant cells – including pericytes, immune cells, and bone marrow-derived cells – contribute to vascular growth (28), (29), (30), (31). This heterotypic interaction highlights the complexity of angiogenesis as a dynamic and cooperative process (1).

Given its central role in tumor survival, angiogenesis has become a major therapeutic target. However, clinical outcomes are often limited by resistance mechanisms, including increased invasiveness and reliance on vascular co-option (32).

Hallmark 6: Deregulating cellular metabolism

An additional hallmark of cancer involves the reprogramming of cellular energetics, commonly referred to as deregulating energy metabolism. This capability reflects the ability of tumor cells to adapt their metabolic pathways to support sustained growth and survival under diverse and often hostile conditions. Non-proliferative or transitorily proliferative normal cells in their particular tissue ecosystems typically depend either on oxidative phosphorylation in mitochondria or, in special cases, on glycolysis, so as to produce energy from glucose metabolism (2). In contrast, many cancer cells rely on glycolysis even in the presence of oxygen, a phenomenon known as the Warburg effect (1). Although this pathway is less efficient in terms of ATP yield, it provides a critical advantage by generating metabolic intermediates that are diverted into biosynthetic pathways, supporting the synthesis of nucleotides, amino acids, and lipids required for rapid cell proliferation (1).

To compensate for reduced ATP efficiency, cancer cells increase glucose uptake through upregulation of transporters such as GLUT1 (1). In parallel, hypoxic conditions within the tumor microenvironment stabilize transcription factors such as HIF-1α and HIF-2α, which upregulate genes associated with glycolysis and glucose transport, reinforcing the glycolytic phenotype (33), (34), (35), (36).

Importantly, tumor metabolism is highly heterogeneous and adaptable. Cancer cells often function as metabolic hybrids, utilizing both glycolysis and oxidative phosphorylation depending on environmental conditions. Beyond glucose, cancer cells rely on additional nutrients from both circulation and the tumor microenvironment (37). In addition, tumors can exhibit metabolic symbiosis, where hypoxic cells produce lactate that is subsequently utilized by neighboring oxygenated cells as an alternative energy source (38), (39), (40). Furthermore, non-cellular factors play an important role in shaping the TME. These include variations in oxygen availability, acidosis, and changes in the local concentrations of amino acids (2). This metabolic plasticity allows cancer cells to dynamically adapt to fluctuations in oxygen, nutrient

availability, and therapeutic stress, with processes such as autophagy enabling survival under adverse conditions (2), (1).

Hallmark 7: Unlocking phenotypic plasticity

It is increasingly evident that the classical clonal model of cancer evolution, based solely on stepwise genetic mutations, is incomplete. Single-cell analyses have revealed that tumors are not only genetically heterogeneous but also exist in a wide range of phenotypic states. This diversity is driven by phenotypic plasticity, an acquired capability that allows cancer cells to dynamically alter their identity in response to internal and external pressures, thereby contributing to tumor progression, metastasis, and therapeutic resistance (2).

Phenotypic plasticity can be broadly divided into intra-lineage and trans-lineage forms. Intra-lineage plasticity refers to changes within the same developmental lineage, including dedifferentiation into more stem-like states, differentiation arrest, and transitions between cancer stem cell-like populations. These states are highly dynamic and often reflect reactivation of developmental or regenerative programs (2).

Trans-lineage plasticity involves more profound identity changes across distinct cellular lineages. The most prominent example is epithelial-mesenchymal plasticity (EMP), where epithelial cells acquire mesenchymal traits associated with increased motility and invasiveness. Unlike normal developmental transitions, cancer cells often occupy hybrid states with mixed epithelial and mesenchymal features, enhancing adaptability and metastatic potential (2).

Importantly, phenotypic plasticity is not restricted to cancer cells but is also a feature of the tumor microenvironment, where immune cells such as tumor-associated macrophages and neutrophils, as well as cancer-associated fibroblasts, exhibit dynamic functional states that can either support or suppress tumor progression. This creates a highly adaptable and interactive ecosystem that enhances tumor resilience (2).

The molecular basis of plasticity arises from the interaction between genetic alterations and epigenetic regulation alongside extrinsic signals from the tumor microenvironment, including hypoxia, metabolic stress, nutrient gradients, and inflammatory cues, all of which continuously reshape cellular states (2).

This dynamic adaptability has major functional consequences, enabling cancer cells to bypass multiple hallmarks, including invasion, immune evasion, and metabolic reprogramming. Most critically, phenotypic plasticity underlies therapy resistance by allowing tumor cells to shift into states that are less sensitive to treatment, rather than relying solely on genetic mutations. From a therapeutic perspective, this plasticity makes cancer particularly difficult to target with single-pathway interventions (2).

Hallmark 8: Evading immune destruction

It is now well established that evading immune destruction represents a hallmark of cancer that reflects the capacity of tumor cells to escape detection and elimination by the immune system. This concept is grounded in the idea of immune surveillance, which proposes that immune cells continuously monitor

tissues and eliminate nascent transformed cells before they develop into clinically detectable tumors. Experimental evidence from mouse models supports this framework, as the absence of key immune effector populations - such as CD8+ cytotoxic T lymphocytes, CD4+ Th1 helper T cells, or natural killer cells - leads to increased tumor incidence and accelerated tumor growth. Clinical observations in humans further reinforce this concept, since tumors with high infiltration of cytotoxic immune cells are often associated with improved prognosis, whereas immunosuppressed transplant recipients may develop donor-derived malignancies, suggesting prior immune control of tumor growth (2), (41), (1), (42).

Tumors that eventually become clinically apparent must therefore escape this immune pressure through a process known as immunoediting, in which the immune system actively shapes tumor evolution. Highly immunogenic cancer cell clones are preferentially eliminated, leaving behind variants with reduced immunogenicity that are less detectable by immune cells. These surviving clones can subsequently expand and form tumors capable of progressing in immunocompetent hosts. Beyond this selection-based mechanism, cancer cells also actively suppress immune responses by creating an immunosuppressive microenvironment. This includes secretion of inhibitory cytokines such as TGF-beta, which impairs cytotoxic T cell and natural killer (NK) cell function, as well as the recruitment and polarization of immunosuppressive immune populations such as regulatory T cells, myeloid-derived suppressor cells (MDSCs), which collectively suppress anti-tumor immunity and support tumor progression (2), (1), (43), (44), (45), (46).

Tumor-associated macrophages (TAMs) are an important immunosuppressive component of the tumor microenvironment and can adopt a broad phenotypic spectrum ranging from tumor-antagonizing to tumor-promoting states. Tumor-promoting TAMs suppress adaptive immune responses and contribute to tumor progression (2). In addition, tumor cells can evade macrophage-mediated phagocytosis through the CD47-SIRPα axis. CD47, which is frequently overexpressed on cancer cells, binds SIRPα on macrophages and delivers an inhibitory signal, preventing phagocytosis and allowing tumor cells to escape innate immune clearance (47). Blocking CD47 or SIRPα can disrupt this interaction and enhance macrophage-mediated elimination of tumor cells (48).

Dendritic cells (DCs) take up tumor antigens and mature before migrating to lymphoid organs, where they present these antigens on MHC class I molecules through cross-presentation to prime tumor-specific CD8+ T cells. This process initiates an adaptive immune response capable of recognizing and eliminating tumor cells (49). The PD-1/PD-L1 pathway can subsequently suppress this response when PD-L1 expressed by tumor cells engages PD-1 on activated T cells, reducing their antitumor activity (50). Antibodies that block PD-1 or PD-L1 can disrupt this interaction and restore T-cell function, allowing immune cells to more effectively attack tumor cells. CTLA-4 regulates an earlier stage of the immune response by competing with the co-stimulatory receptor CD28 for CD80 and CD86 on antigen-presenting cells, thereby limiting T-cell activation during initial priming. Consequently, simultaneous blockade of CTLA-4 and PD-1/PD-L1 can target complementary stages of the antitumor immune response, enhancing T-cell activation during priming while preventing subsequent immune suppression within the tumor microenvironment (50).

Ultimately, the development of immune checkpoint inhibitors has provided clinical evidence that disrupting mechanisms responsible for limiting T-cell activity can restore antitumor immune responses, highlighting the importance of immune evasion in cancer progression (2), (51).

The tumor microenvironment thus becomes a key regulator of immune escape, where cancer cells and immune cells engage in continuous bidirectional interactions. Importantly, immune evasion is not solely a passive consequence of reduced immunogenicity, but an actively maintained state shaped by both genetic and environmental pressures (2), (1).

Hallmark 9: Activating invasion and metastasis

Activating invasion and metastasis represents a hallmark capability that enables cancer cells to escape the primary tumor, invade surrounding tissues, and ultimately disseminate to distant organs where they can establish secondary tumors. This process is now understood as a highly coordinated, multistep sequence known as the invasion–metastasis cascade (52), (53). It begins with local invasion, where cancer cells breach the boundaries of the primary tumor and infiltrate adjacent tissues, followed by intravasation into blood or lymphatic vessels. Circulating tumor cells then survive transport through the vasculature, eventually exiting at distant sites through extravasation. After arrival, disseminated cells may form micrometastases, which can remain dormant or progress to the final and most critical step - colonization, in which they expand into clinically detectable secondary tumors (2), (1).

A central mechanism driving this invasive behavior is epithelial-mesenchymal transition (EMT), a developmental program co-opted by cancer cells. During EMT, epithelial cells lose their stable, adhesive properties and acquire mesenchymal traits associated with motility and invasiveness (54), (55), (56), (57), (58). This is accompanied by downregulation of E-cadherin and upregulation of N-cadherin, facilitating detachment and migration. Importantly, this process is reversible, and metastatic cells can undergo mesenchymal-epithelial transition (MET) after reaching distant organs, enabling them to re-establish epithelial-like growth and form organized secondary tumors (59), (1).

A key feature of metastasis is that dissemination does not guarantee successful tumor formation. Many circulating or disseminated cancer cells enter a state of dormancy, which may persist for extended periods due to immune surveillance, lack of angiogenesis, nutrient limitation, or inhibitory microenvironmental signals (1), (52), (53), (60), (61), (62). For metastasis to succeed, these cells must eventually overcome environmental constraints and adapt to the conditions of the new tissue niche (1).

Overall, invasion and metastasis arise from a combination of cellular plasticity, EMT/MET-driven reprogramming, and dynamic interactions with the tumor microenvironment, making this process one of the most complex and clinically significant hallmarks of cancer.

Metal-organic Frameworks

Over the past two decades, MOFs have experienced rapid development, emerging as a highly versatile class of crystalline materials with precisely tunable structures. MOFs are constructed from

metal-containing nodes, SBUs, which are connected by multitopic organic linkers to form extended three-dimensional networks (63). This modular assembly gives rise to highly ordered and exceptionally porous architectures, enabling applications across diverse fields, including gas storage, catalysis, and chemical separation (64). Importantly, the same structural features that make MOFs attractive in materials science – high surface area, tunable pore size, and chemical versatility – also underpin their growing relevance in biomedical contexts (65), (3).

A key advance in MOF chemistry has been the development of rational design principles, often described within the framework of reticular chemistry. Rather than relying on simple node-and-linker assembly, it has been shown that the use of rigid, geometrically well-defined building units – such as square-planar or octahedral SBUs – enables more predictable and stable framework formation (63). Within this context, the concept of isoreticular synthesis has proven particularly powerful. This strategy involves systematically varying the length or functionality of organic linkers while preserving the underlying network topology, allowing the creation of families of structurally related MOFs with tunable pore dimensions and chemical environments (66). Topology, in this sense, refers to the fundamental connectivity pattern of the framework - the geometric "blueprint" that dictates how SBUs and linkers are arranged in space (3).

Tunability is particularly relevant for biomedical applications, where pore size and surface functionality directly influence drug loading capacity, diffusion behavior, and interactions with biological molecules (67), (68), (3).

Another major development in MOF chemistry is post-synthetic modification (PSM), which enables chemical transformation of a pre-formed framework without disrupting its overall structure. Through PSM, functional groups can be introduced, altered, or exchanged within the pores or on the framework backbone, providing a powerful tool for tailoring MOFs to specific applications (69). In the context of biomedicine, this approach is particularly valuable, as it allows the incorporation of targeting ligands, therapeutic molecules, or stimuli-responsive functionalities after synthesis, thereby enhancing selectivity and functionality without requiring complete redesign of the material (3), (5).

Despite their structural advantages, early MOFs often suffered from limited chemical stability, particularly in the presence of moisture or reactive solvents. This challenge has been addressed through the development of more robust frameworks, including zeolitic imidazolate frameworks such as ZIF-8 (Zn(2-methylimidazolate)$_2$), which exhibit exceptional stability under harsh conditions, including exposure to boiling solvents and basic environments. Such stability is critical for biological applications, where materials must withstand complex aqueous and physiological conditions without degradation (3), (70).

Recent advances have further expanded the design space of MOFs beyond simple periodic structures. For example, multivariate MOFs (MTV-MOFs) incorporate multiple functionalized linkers within a single framework, enabling heterogeneous chemical environments within the same material (71). This increased complexity more closely resembles biological systems, where multiple functionalities operate simultaneously and cooperatively. Similarly, the development of MOF nanocrystals and their assembly

into higher-order structures have opened new possibilities for controlling size, morphology, and surface properties – parameters that are particularly important for interactions with cells and tissues (7), (72), (73).

Altogether, these advances demonstrate that MOF chemistry has evolved from simple porous materials toward highly programmable platforms with precise control over structure, composition, and functionality (3). This level of tunability is especially relevant in the context of cancer research, where complex and dynamic biological systems require equally adaptable therapeutic strategies (5). By enabling controlled delivery, environmental responsiveness, and multifunctional integration, MOFs provide a versatile foundation for designing systems capable of interacting with multiple aspects of tumor biology, including drug resistance, microenvironmental modulation, and immune response regulation (5), (6).

Application of MOFs

The properties of a MOF – its metal node, linker chemistry, pore dimensions, and surface functionalization – are not fixed givens but design choices, and each can be selected against a particular feature of the tumor microenvironment. This raises the operative question of this section: not whether MOFs can carry a therapeutic payload, but how their tunable properties can be matched to the specific vulnerabilities a tumor presents. To examine how that matching is done in practice, this section works through three representative studies, each pairing a MOF system to a distinct microenvironmental target, before drawing them together in Table 1 and assessing what the body of evidence does and does not establish.

Each of these systems is engineered against a specific feature of the tumor microenvironment, and each of those features is itself the downstream product of a cancer hallmark. The extracellular and endosomal acidity that triggers release in both the MS@MOF vaccine and the CAD@ZIF-8-FA system arises from the deregulated cellular metabolism of Hallmark 6, whose reliance on aerobic glycolysis raises lactate and proton concentrations and produces the gradients of acidosis that characterize the tumor interstitium (2). The CD47 signal and the M2-polarized macrophage population that the Hf-DBP system reverses are manifestations of evading immune destruction (Hallmark 8), by which tumors suppress both innate and adaptive surveillance (2). Folate receptor overexpression, which the FA-targeted system uses to home to tumor cells, fits this scheme less cleanly: it is not the consequence of any single hallmark but a targeting handle exploited for selectivity – a distinction that anticipates a broader pattern in these designs, where MOFs more often read out the byproducts of hallmark activity than act on the hallmarks themselves.

Beyond geometry and pore chemistry, the identity of the metal node is itself a design variable, and a handful of metals – Fe^{3+}, Zr^{4+}, Hf^{4+}, and Zn^{2+} – recur as the biomedical workhorses because they balance framework stability against acceptable toxicity. Which metal-linker pairings hold together can be anticipated from Pearson's hard-soft acid-base (HSAB) principle. Hard, high-valent metals such as Zr^{4+}, Hf^{4+}, and Fe^{3+} form stable bonds with hard carboxylate linkers, while softer ions such as Zn^{2+} pair with softer azolate linkers, as in the ZIF-8 systems above (5). Toxicity constrains the same choice from the other side: across the most-studied MOFs, those built on Fe, Co, and Al rank lowest in toxicity, those on

Zr, Mg, Ni, and Zn intermediate, and those on Cu and Mn highest (8), a tiering that rests on the oral LD50 values reported for the constituent metal ions (9). Yet stability predicted from HSAB does not reliably survive contact with blood: physiological phosphate, a hard base present at high concentration, competes for the metal coordination sites that hold the framework together, so a MOF that is robust on the bench can degrade in circulation (5). This is the general principle underlying the phosphate vulnerability noted for each of the ZIF-8 systems above, which are specific instances of it rather than separate observations.

The first study considered here was conducted by Li et al. (4). Building on the clinical success of checkpoint blockade (77), (78), they built a core–shell particle (MS@MOF) in which a mesoporous silica core is enclosed by a ZIF-8 shell, then loaded the model antigen ovalbumin (OVA) and the immunopotentiator polyinosinic-polycytidylic acid (polyIC) into the silica pores. They tested several configurations for cellular uptake, pH-triggered degradation, and dendritic-cell activation and antigen presentation in vitro, and assessed the lead formulation together with PD-1 blockade. They found that the wide pores of the silica core could hold large biomolecules such as protein antigens and nucleic-acid adjuvants, while the ZIF-8 shell stays closed at extracellular pH (7.4) and dissolves only in the acidic endosome, releasing both cargoes into the cytoplasm and driving endosomal escape (4). Efficacy was shown in vitro in BMDCs and in vivo in a subcutaneous E.G7-OVA lymphoma model in C57BL/6 mice. Unfortunately, no clinical data exist for this system. Despite the promising results, Li et al.'s study has some limitations. Firstly, OVA is a strong model antigen rather than a patient-derived neoantigen, so the immune response may overstate what a clinical vaccine would achieve. Secondly, subcutaneous delivery leaves open how the particle would behave in blood circulation in human bodies.

Ni et al. targeted the same hallmark, evading immune destruction, but through a different route. The researchers based their study on the possible method of treating cancer cells with imiquimod (IMD), a molecule that activates the toll-like receptor-7 (TLR-7) pathway and can switch the TAMs (specifically M2 macrophages to M1 macrophages) (74), (48), thereby promoting phagocytosis of tumor cells and releasing tumor antigens (75), (76). They also used a second strategy with anti-CD47 antibodies. However, to address the inadequate antitumor efficacy and undesired side effects of injecting the toxic IMD and α-CD47, they designed a hafnium-based porphyrinic MOF called Hf-DBP, comprised of hafnium SBUs and photosensitizing 5,15-di(p-benzoato)porphyrin linkers. In their work, IMD@Hf-DBP/αCD47 was constructed by Hf-DBP surface modification, IMD loading, and αCD47 adsorption. Hf promotes a strong radiodynamic therapy (RDT) effect because its high atomic number (Z = 72) gives Hf-based MOFs strong X-ray absorption (5). This allows them to capture more radiation energy and efficiently transfer it to photosensitive ligands, which then generate larger amounts of singlet oxygen and other ROS (80). IMD@Hf-DBP/αCD47 combined with X-ray irradiation elicited a strong RT-RDT effect that caused the immunogenic cell death (ICD) of tumor cells and improved the immunomodulation effects of the TLR-7 agonist and the CD47 blocker. In their bilateral CT26 tumor model, the team combined their nMOF therapy with αPD-L1 therapy and observed systemic eradication of primary and distant tumors, demonstrating an effect on evading immune destruction (Hallmark 8) (48). However, this evidence remains preclinical, as the study was conducted in a murine CT26 tumor model and did not

provide human clinical data. In addition, the study used intratumoral administration, so the results do not establish how effectively this system could perform following systemic delivery.

Yan et al. targeted the third hallmark, resisting cell death, by using doxorubicin (DOX) to restore cytotoxicity, with the delivery system built around the acidity of the tumor microenvironment and the even lower pH of intracellular compartments. Rather than loading the drug directly, they first reacted it with cis-aconitic anhydride to form a pH-sensitive prodrug, CAD. This step does two things at once: the prodrug carries two carboxyl groups that strengthen its coordination with ZIF-8 and also serve as attachment points for folic acid (FA) on the particle surface, giving the system a tumor-targeting ligand (79). Release then proceeds in three acid-dependent stages. The pH-labile bond linking CAD to FA cleaves first, exposing the ZIF-8 nanoparticle; the acidic environment next degrades the ZIF-8 framework and releases CAD; finally the cis-aconityl linker breaks to regenerate active DOX, which blocks DNA and RNA synthesis (79). The design suits controlled DOX delivery for two reasons that follow from that chemistry: the carboxyl groups improve loading into ZIF-8 while doubling as FA conjugation sites, and the authors report that the FA layer shifts the surface charge in a way that lowers nonspecific uptake by healthy cells. The system was tested in vitro in MDA-MB-231 breast cancer cells alongside MCF-10A normal cells, and in vivo in huPBMC-NCG mice bearing subcutaneous MDA-MB-231 tumors. The authors reported stronger tumor suppression from CAD@ZIF-8-FA than from free DOX, with lower toxicity in treated animals (79); these findings remain entirely preclinical. The main gap concerns carrier stability in circulation: the system was given intravenously, yet the study does not examine whether the ZIF-8 framework degrades prematurely in blood, where phosphate competes for the zinc coordination sites that hold the framework together – the same vulnerability that recurs across the ZIF-8 systems reviewed here.

Table 1.

MOF system	TME target	Mechanism	Author
MS@MOF + OVA/polyIC	Acidic endosomal pH	ZIF-8 shell opens in acid → cytosolic co-delivery of antigen + adjuvant, endosomal escape	Li et al.
IMD@Hf-DBP/αCD47	M2 macrophages + CD47 signal	X-ray-triggered: M2→M1 repolarization + CD47 blockade → phagocytosis; synergy with anti-PD-L1	Ni et al.
CAD@ZIF-8-FA	Extracellular + intracellular acidity	Three-stage acid release regenerates active DOX → blocks DNA/RNA synthesis	Yan et al.
MOF system	**Hallmark**	**Evidence Level:**	
MS@MOF + OVA/polyIC	Evading immune destruction	In vitro (BMDCs); in vivo (E.G7-OVA lymphoma, C57BL/6); no clinical data; no clinical data	
IMD@Hf-DBP/αCD47	Evading immune destruction	In vivo (bilateral colorectal tumor model); no clinical data	
CAD@ZIF-8-FA	Resisting cell death	In vitro (MDA-MB-231; MCF-10A control); in vivo (huPBMC-NCG, MDA-MB-231); no clinical data	

Read together, these three studies reveal a consistent logic rather than three isolated results. Two of them attack the same hallmark, evading immune destruction, from opposite arms of the immune system – the MS@MOF vaccine engaging adaptive immunity through antigen presentation, the Hf-DBP system engaging innate immunity through macrophage repolarization and phagocytosis – which shows that a single hallmark offers multiple, mechanistically distinct points of attack. A shared vulnerability also recurs: across the ZIF-8 systems, framework stability in circulation is undercut by the same phosphate competition described earlier as a general principle. More fundamentally, a common pattern holds across all three - these systems exploit the *consequences* of hallmark activity, the acidity and the immune signals a tumor produces, rather than inhibiting the hallmark programs themselves. And the evidence remains

uniformly preclinical: every system here stops at the animal model, and field-wide only two MOF platforms, RiMO-301 and RiMO-401, have reached human trials, both non-targeting and both delivered exclusively by intratumoral injection (8) – a reminder of how far the clinical frontier still sits from the actively targeted designs, several of them systemically administered, that this section has examined.

CONCLUSION

The findings presented throughout this review suggest that the significance of MOFs in cancer therapy extends beyond their role as simple nanocarriers. Rather than functioning only as passive delivery systems, MOFs increasingly appear to operate as programmable therapeutic platforms capable of influencing multiple biological processes simultaneously. This multifunctionality is particularly important in cancer, where tumor progression is driven not by a single mechanism, but by highly interconnected hallmarks such as immune evasion, metabolic adaptation, angiogenesis, and therapeutic resistance.

One important trend observed across the reviewed studies is the growing shift from monofunctional therapies toward integrated combination strategies. Traditional chemotherapy often relies on direct cytotoxicity alone, whereas many MOF-based systems combine controlled drug delivery with immune activation, photodynamic therapy, radiodynamic therapy, or metabolic modulation. The relationship between these approaches appears highly synergistic. For example, radiodynamic therapy mediated by MOFs not only damages tumor cells through reactive oxygen species generation, but also promotes immunogenic cell death, thereby linking localized tumor destruction with systemic immune activation. This suggests that future cancer therapies may increasingly depend on coordinated multi-pathway intervention rather than isolated treatment modalities.

Another major principle revealed in the literature is the importance of tumor microenvironment responsiveness. Many MOF systems are specifically engineered to respond to acidic pH, hypoxia, oxidative stress, or elevated glutathione concentrations within tumors. This reflects a broader conceptual transition in oncology: instead of attempting to eliminate cancer through uniform systemic exposure, emerging therapies aim to exploit the unique biochemical conditions of tumor tissues themselves. In this context, MOFs demonstrate a particularly strong advantage because their structural tunability allows simultaneous control over cargo loading, degradation behavior, targeting, and environmental responsiveness.

The reviewed findings also reveal a strong connection between structural complexity and therapeutic adaptability. Advances such as MTV-MOFs, hierarchical core-shell architectures, and nanoscale surface engineering increasingly mimic the multifunctional organization observed in biological systems. This relationship suggests that future therapeutic success may depend less on maximizing the potency of a single drug and more on designing integrated systems capable of dynamically interacting with evolving tumor environments. In this sense, MOFs represent not only pharmaceutical technology, but also a materials-based strategy for managing cancer heterogeneity and phenotypic plasticity.

However, the central obstacle here is that the conditions which make a MOF effective in a cell culture or a subcutaneous mouse tumor are very different from those in the human circulation. Once a MOF enters the bloodstream, serum proteins adsorb onto its surface within seconds to form a protein corona, and this biomolecular layer can bury the targeting ligands conjugated to the particle, cancelling the active targeting and redirecting the MOF toward non-specific uptake and immune clearance (5). Moreover, framework stability is challenged. As noted above, physiological phosphate competes for the metal coordination sites that hold the framework together, so a MOF can begin to degrade before it reaches the tumor. Also, it is difficult to control the precise parameters of MOFs, such as density, surface area, and pore diameter, at a manufacturing scale, so we have to expect defects along the way. Finally, the metal nodes that make MOFs versatile raise a regulatory question that preclinical efficacy does not answer: the long-term safety of the degradation products and the accumulation of heavy metals such as hafnium or zirconium in organs over time. These barriers are not arguments against MOF therapeutics, but they mark the distance between a promising animal result and a viable human therapy.

Several limitations of this review itself should be discussed as well. First, this paper was based on studies generally showing positive outcomes, and does not take into account those articles where trials showed rather unfulfilling results. Thus, the visible literature skews toward success and likely overstates the field's overall reliability. Second, experimental models differ so widely – across immortalized lines, primary cells, and 3D organoids, assessed with different cytotoxicity assays and tumor models – that efficacy claims from different laboratories cannot be compared on a common footing. Third, the field is expanding rapidly, so any snapshot of it dates quickly. A further and more troubling caution, as reported in a recent methodological review, is that a substantial number of entirely falsified MOF-in-medicine publications, produced by paper mills, have entered the literature (5) – which argues for real caution in weighting historical results and for anchoring conclusions, wherever possible, to primary studies whose data can be scrutinized.

Despite these challenges, the broader trajectory of current research strongly supports the continued development of MOF-based therapeutics. The integration of immunotherapy, nanotechnology, and reticular chemistry suggests that future oncology may increasingly rely on adaptive therapeutic systems capable of responding dynamically to tumor evolution. Particularly promising directions include the combination of MOFs with immune checkpoint blockade, gene-editing technologies, and externally controlled activation methods such as light, ultrasound, or X-rays.

What the collective findings of this review support is narrower than a change in therapeutic philosophy, but not trivial: MOFs offer a design approach in which a carrier can be tuned to respond to the specific biochemical conditions of tumor tissue – its acidity, its immune signals – rather than delivering a drug uniformly throughout the body. By pairing structural programmability with this biological responsiveness, MOFs make it possible to build systems that engage tumor conditions rather than simply exposing cells to a cytotoxic agent. Whether that design advantage translates into clinical benefit remains unresolved, and on the present evidence it is a question for future work rather than a settled result.

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