Himalayan Physics

Recent advances in metal-organic frameworks for anticancer nanodrug delivery

https://doi.org/10.3126/hp.v13i1.78192

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Abstract: Cancer is a leading cause of death in the 21^{st} century. It results from the uncontrolled growth of cells that disrupt normal organ function. Traditional treatments like radiotherapy, chemotherapy, and surgery are commonly used. These can damage healthy cells and cause unwanted side effects. Metal-organic frameworks (MOFs) have emerged as an innovative solution in cancer therapy. They offer advancements in drug delivery systems. MOFs have unique properties, including high surface area, tunable structures, and the ability to encapsulate various therapeutic agents. They provide more efficient, targeted, and controlled drug delivery. The selective targeting capabilities of MOFs allow for direct treatment of cancer cells. This minimizes damage to healthy tissue and reduces adverse effects of conventional therapies. While MOFs hold great potential in cancer treatment, challenges remain. These include scalability, stability, bio-compatibility, and safety in clinical settings. Ongoing research is focused on overcoming these challenges. With further advancements, MOFs could revolutionize cancer treatment. They offer safer, more effective alternatives to current therapies, improving patient outcomes.

Keywords: Metal-organic frameworks (MOFs) • Cancer Therapy • Targeted Drug Delivery • Nanomedicine • Biocompatibility

Recieved: 2025-04-30 **Revised: 2025-05-19** **Published: 2025-05-20**

I. Introduction

Cancer continues to pose a significant threat to global health, affecting millions of individuals each year. In 2020, around 19.3 million new cancer cases were reported worldwide, with nearly 10 million deaths attributed to the disease [1]. By 2030, cancer-related mortality is projected to rise to 13.1 million [2], emphasizing the urgent need for advancements in research and healthcare interventions. As a complex disease, cancer causes serious disruptions to the body's normal physiological processes [3]. Given its severe complications, exploring effective treatment options remains essential. Traditional approaches such as radiotherapy, chemotherapy, and surgery remain widely used; however, they can also harm healthy cells,

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leading to unwanted side effects. Therefore, there is a pressing need to develop advanced treatment strategies that are both effective and less harmful to the body [4]. New treatment approaches, including targeted drugs, biological molecules, and immune-based therapies, are being explored to combat cancer. Although these methods have not yet achieved the expected level of effectiveness in reducing mortality rates and extending survival for metastatic cancer, they hold promise for improving treatment outcomes in the future [1].

Cancer targeting has emerged as a promising new biotherapy for cancer treatment. This approach focuses on delivering anticancer drugs directly to tumor tissues, which helps increase local drug concentration, enhance treatment effectiveness, and significantly reduce side effects. To achieve this selective drug delivery, a specialized method known as the Targeting Drug Delivery System (TDDS) is used, ensuring that the medication reaches cancer cells more efficiently while minimizing damage to healthy tissues [5]. The development of the TDDS relies heavily on the design of advanced nanocarrier materials that can effectively transport and release drugs at tumor sites. Various nanocarriers, such as chitosan, hyaluronic acid (HA), polyethylene glycol (PEG), lipoproteins, and human serum albumin (HSA), are being explored for their ability to enhance drug stability and targeting efficiency. Additionally, graphene, mesoporous silica nanoparticles (MSNs), and metal-organic frameworks (MOFs) offer high drug-loading capacities and controlled release mechanisms, making them promising candidates for precise drug delivery. These nanocarriers play a crucial role in improving the effectiveness of cancer treatments by ensuring that drugs specifically reach tumor cells while minimizing side effects on healthy tissues [6, 7].

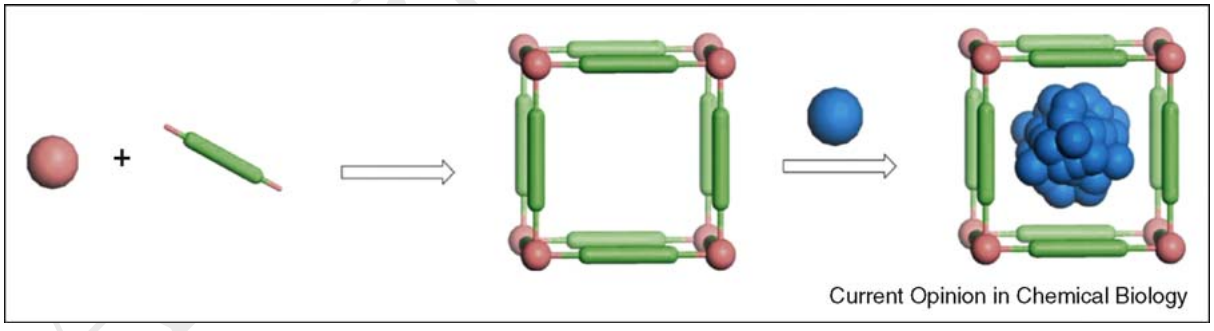

Figure 1. MOFs form via self-assembly; drugs load by encapsulation. One unit of the infinite structure is shown [8].

Metal-organic frameworks (MOFs) are porous materials constructed from metal nodes coordinated with organic linkers, forming extended network structures, as illustrated in Fig. 1 [9]. MOFs exhibit a diverse range of framework structures [10] and are known for their high porosity, which can reach up to 90% [11]. They possess large BET surface areas [12] and customizable pore structures [13], allowing for flexibility in design. Additionally, MOFs have low crystal density and are renowned for their high thermal and chemical stability [14], making them both versatile and durable materials. These exceptional properties make MOFs ideal for a wide range of applications, including gas storage and separation,

catalysis, drug delivery, purification, water harvesting, and enzyme immobilization [15–17].

MOFs have gained significant attention as potential drug delivery materials due to their nontoxicity, biocompatibility, and safety for use within biological systems. Their highly porous structure provides a large surface area, which allows for substantial drug-loading capacities and controlled release. Additionally, the small size of MOFs enables efficient cellular uptake, improving the targeted delivery of drugs to specific areas within the body. MOFs also offer versatility, as they can be tailored in terms of size, shape, and chemical composition, making them adaptable for a wide range of drug delivery applications [8].

Moreover, MOFs can be incorporated into stimuli-responsive drug delivery systems (DDS), which are particularly effective in targeting cancer cells. As explained by Cai and colleagues [18], these DDSs can be activated through two primary mechanisms: one by enhanced permeability and retention at the tumor site, and the other through receptor-ligand interactions. Upon injection, MOFs or other nanomaterials in DDSs accumulate in the tumor and are activated by specific internal stimuli, such as the lower pH or higher temperature found in the tumor microenvironment. Alternatively, external stimuli, including light, magnetic fields, temperature, or ultrasound, can also trigger the release of the drug at the tumor site. This dual approach: internal and external enhances the precision of drug delivery, enabling continuous drug release and increasing the effectiveness of biomedical applications, particularly in cancer treatment [18, 19].

The primary objective of this review is to explore the application of MOFs in cancer treatment, with a specific focus on their potential as targeted drug delivery systems. This paper aims to highlight the advantages of MOFs over traditional drug delivery methods, discuss various synthesis and functionalization strategies, and evaluate their effectiveness, challenges, and future prospects in improving the precision and efficiency of cancer therapeutics.

II. Development of MOFs

In the 1960s, Tomic and colleagues began reporting structures that laid the foundation for Metal-organic frameworks [20]. However, it wasn't until the early 1990s that MOF research experienced a significant surge, particularly following the rediscovery of MOF-based porous materials by Omar Yaghi and his research group [21]. The true prominence of metal-organic frameworks became evident with the discovery of MOF-5 by Professor Omar Yaghi [22]. MOF-5 made a groundbreaking impact by shattering the historical world record for porosity, boasting an extraordinary surface area of 6,500 m^2/g at that time. This discovery has since been widely acknowledged by numerous researchers as the most prominent example of a metal-organic framework [21]. Various properties, including X-ray single crystal structure determination and gas sorption properties, were reported for the first time in the case of MOF-5. This marked the initiation of a golden age in the field of MOF development [22].

MOF-2, disclosed in 1998 with the composition Zn(BDC)(H2O) (BDC = 1,4-benzenedicarboxylate), stood out as an early MOF demonstrating permanent porosity and featuring a Type-1 adsorption isotherm. This particular MOF showcased Langmuir surface areas ranging from 270 to 310 m^2/g, coupled with micropore volumes between 0.094 and 0.086 cm^3/g [23, 24]. In the early stage of development, MOFs follow a chronological numbering system based on their discovery. Later MOFs adopt names derived from the universities where they were synthesized, such as UiO-66 (University of Oslo), MIL (Materials Institute Lavoisier), HKUST (Hong Kong University of Science and Technology), etc., reflecting the connection between the materials and their originating institutions [21].

In recent years, significant efforts have been dedicated to synthesizing MOFs by carefully selecting inorganic nodes and organic linkers, leading to a variety of structures with diverse functionalities. Traditionally, MOFs have been synthesized on a small scale using hydrothermal or solvothermal methods with conventional electrical heating [26]. However, recent advancements, such as the precursor approach and kinetically tuned dimensional augmentation strategy, have opened new pathways for designing novel MOFs with unique structures and properties [26, 27]. To accelerate crystallization and produce uniform, smaller-sized crystals, researchers have explored alternative synthesis techniques. Methods like microwave-assisted synthesis, electrochemical synthesis, sonochemical synthesis, mechanochemical synthesis, and spray-drying synthesis have been developed. These approaches not only reduce synthesis time but also enhance MOF quality, making them more suitable for industrial applications [27]. So far, over 12,500 MOF structures have been documented in the Cambridge Crystallographic Data Centre (CCDC) [28].

III. Pioneering Drug Delivery Systems

In 2006, Horcajada and colleagues investigated the first group of MOFs suitable for drug delivery systems [29]. This pioneering family includes two key types, MIL-100 and MIL-101, where MIL stands for Materials of Institut Lavoisier. These MOFs were synthesized using carboxylic acid groups as organic ligands and trivalent metals as structural clusters. The MIL family exhibits remarkable potential for drug delivery due to its combination of large, well-defined pores (25–34 Å), exceptionally high surface areas (3100–5900 m^2/g) [8], and the capacity to form hybrid frameworks with functional groups, all of which contribute to their enhanced performance as efficient drug carriers [25, 29].

Horcajada and colleagues were the first to demonstrate the exceptional ability of porous MOFs for drug encapsulation and controlled release, specifically using MIL-100 and MIL-101. Fig. 2 shows the structure of Cr-MIL-100 and Cr-MIL-101. These materials exhibited outstanding ibuprofen absorption capacities [25]. The loading process involved dissolving 100 mg of MIL-100 and 100 mg of MIL-101 in 10 mL of hexane, followed by stirring in the presence of 200 mg and 400 mg of ibuprofen, respectively.

Ultraviolet-visible (UV-Vis) spectroscopy confirmed that MIL-100 could hold 0.35 g of ibuprofen per gram of material, while MIL-101 had an even higher capacity of 1.4 g of ibuprofen per gram of material [29].

Despite these high loading capacities, structural analysis using X-ray diffraction (XRD) confirmed that the MOF framework remained intact. This is a crucial finding since it means that even small amounts of these materials can be used to administer large doses of medication. The release of ibuprofen from the MOFs was carefully controlled, with complete drug delivery occurring within three days for MIL-100 and six days for MIL-101. This controlled release profile is particularly beneficial, as it helps to minimize the side effects often associated with conventional ibuprofen administration [29].

To assess their drug delivery performance, MIL-100 and MIL-101 were compared with MCM-41, a material with a similar porous structure and a pore diameter of 36 Å. MIL-100 and MCM-41 exhibited comparable ibuprofen loading capacities and release rates. However, MIL-101 demonstrated a significantly superior performance, with a drug content four times higher than that of MCM-41. Additionally, the ibuprofen release from MIL-101 was much slower, taking six days compared to just two days for MCM-41. This extended release profile and higher drug-loading capacity make MIL-101 particularly advantageous for delivering larger pharmaceutical molecules, offering potential benefits for advanced drug delivery applications [29]. Due to toxic chromium, these MOFs have limited use in drug delivery. MIL-101(Fe), a safer and biocompatible alternative, offers a more suitable option [30].

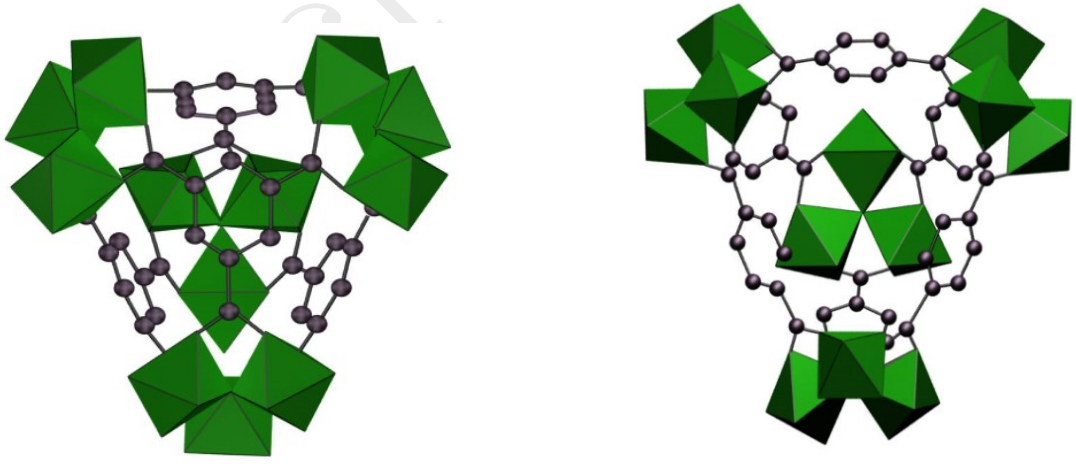

Figure 2. The pioneering structure of MOFs that revolutionized drug delivery [(a) Cr-MIL-100 and (b) Cr-MIL-101] [25]

The Férey group demonstrated controlled drug release using MIL-53, a flexible MOF from the MIL family. Both MIL-53(Cr) and the less-toxic MIL-53(Fe) showed high ibuprofen loadings (0.220 g/g and 0.210 g/g, respectively). Drug release in simulated body fluid at 37°C was completed in three weeks, due to the framework's flexibility and strong drug–MOF interactions. This slow release makes MIL-53

promising for sustained drug delivery. Overall, MIL MOFs offer higher drug loadings than previously studied materials, and with their tunable porosity and metal versatility, more MOFs are likely to be explored as drug carriers [31].

IV. MOFs as Targeted Anti-Cancer Drug Carriers

MOFs are extensively utilized as customizable theranostic platforms for diagnosing and treating cancer. They support a variety of single-mode therapies, including photodynamic therapy (PDT), photothermal therapy (PTT), chemotherapy, radiotherapy, and immunotherapy. In addition, MOFs enable combined or multimodal approaches that integrate imaging, thermal, and chemotherapeutic treatments for enhanced therapeutic effectiveness [32].

In 2009, Lin and his team investigated the loading of cisplatin into the nanoporous material MIL-101 (Fe) [33]. Cisplatin and its derivatives, which are based on platinum, are commonly used to treat cancers like testicular and ovarian cancer. However, these treatments are often accompanied by serious side effects such as nausea, kidney damage, and suppression of bone marrow [34]. To reduce these harmful effects, a modified form of cisplatin called ethoxysuccinato-cisplatin (ESCP) was loaded into a functionalized version of Fe-MIL-101 [33]. ESCP has shown effectiveness against a variety of cancers, including those of soft tissue, bones, muscles, and blood vessels, offering a potentially safer alternative for treatment. Topotecan (TPT), a drug from the camptothecin (CPT) family, is another chemotherapeutic agent that has been loaded into nanoMOFs. TPT is hydrophobic and only slightly soluble in water, and it's commonly used for treating lung, cervical, and ovarian cancers. However, its effectiveness is limited due to the high toxicity of its carboxylate form and its poor uptake by cells. To overcome these issues, researchers have loaded TPT into various nanocarriers, including MOFs. These studies have shown that this approach reduces the drug's toxicity and improves its ability to be taken up by cells, potentially enhancing its therapeutic effects [35, 36].

An additional application of MOFs in cancer therapy involves loading the anti-cancer drug doxorubicin (DOX) into MIL-100(Fe). DOX is widely used to treat various cancers, including childhood solid tumors, breast cancer, soft tissue sarcomas, myeloblastic leukemias, and lymphomas [37]. However, its clinical use is limited by significant side effects such as nausea, vomiting, hair loss, tissue necrosis, and oral mucositis. Further challenges include early cardiotoxicity leading to heart failure and cardiomyopathy, its tendency to self-assemble in aqueous environments (reducing cellular uptake), and the rapid development of drug resistance in cancer cells [38]. Encapsulating DOX in MIL-100(Fe), a type of metal-organic framework (MOF), offers a promising strategy to overcome these drawbacks. The system demonstrated an initial burst release of 25% within 12 hours, followed by a gradual release that reached 100% over 13.5 days. This controlled release behavior can help maintain therapeutic drug levels for extended periods,

potentially minimizing side effects, reducing dosing frequency, and improving drug effectiveness against resistant cancer cells [25].

5-Fluorouracil (5-FU) is another widely used anti-cancer drug that has been successfully loaded into ZIF-8. This anti-neoplastic agent is employed in the treatment of various cancers, including those affecting the liver, breast, brain, gastrointestinal tract, pancreas, and other solid tumors. However, its clinical application is limited due to significant hematological, gastrointestinal, and dermatological side effects. To address these issues, 5-FU was encapsulated in ZIF-8, a metal-organic framework, to improve its delivery and reduce toxicity [39]. Similarly, the chemotherapeutic agent Camptothecin (CPT) was also loaded into ZIF-8 using a comparable approach. As with other cytotoxic drugs, encapsulating CPT in MOFs aimed to mitigate its adverse effects while enhancing therapeutic potential [40].

The studies demonstrate that MOFs, particularly ZIF-8 and Gd-pDBI, offer effective platforms for pH-responsive delivery of the anti-cancer drug doxorubicin (DOX). DOX was successfully encapsulated in both MOFs, with ZIF-8 showing a high loading efficiency of 52% and selective drug release in acidic environments, which mimics the tumor microenvironment. Release studies confirmed that ZIF-8 remains stable at physiological pH (7.4) but dissociates in more acidic conditions (pH 5–6), allowing targeted drug release at tumor sites while minimizing impact on healthy tissue. Similarly, Gd-pDBI MOF demonstrated enhanced pH-dependent release, with 44% of DOX released at pH 5 over 5 days compared to just 22% at pH 7.4. This selective behavior supports the potential for reduced side effects in healthy cells. In vitro testing on leukemia cancer cells further validated the anti-cancer efficacy of the Gd-pDBI-DOX system, with significant inhibition observed. These findings highlight MOFs as promising, pH-sensitive drug delivery systems for targeted cancer therapy [41, 42].

A promising emerging approach in cancer therapy involves the use of magnetic MOFs for targeted drug delivery. These MOFs possess magnetic properties that enable them to be directed precisely to tumor sites using an external magnetic field, making them particularly useful for treating tumors with known locations. Nimesulide (NIM), an anti-cancer drug used against pancreatic, colorectal, breast, and prostate cancers, was successfully encapsulated in a 3D magnetic MOF to reduce its common side effects, such as gastrointestinal intolerance and ulcers. Compared to earlier systems like mesoporous silica particles (e.g., MCM-41), magnetic MOFs offer a more cost-effective and simpler synthesis method while maintaining strong targeting capabilities. This strategy enhances treatment efficiency by concentrating the drug at the tumor site, potentially reducing systemic toxicity and improving therapeutic outcomes [43].

Photoresponsive therapies—encompassing photothermal therapy (PTT), photodynamic therapy (PDT), and fluorescence imaging—offer promising approaches for precise, minimally invasive cancer treatment, especially when combined with metal-organic frameworks (MOFs) as multifunctional drug delivery platforms. MOFs such as TMPyP@MOF, ZIF-8, MOF@HA@ICG, and Zr(IV)-based porphyrinic MOFs

have demonstrated excellent biocompatibility, targeted delivery, and the ability to integrate diagnostic and therapeutic functions. For instance, GOx/ZIF-8 composites have shown sensitive cancer detection via fluorescence quenching, while MOF@HA@ICG has enabled PTT, FL imaging, photoacoustic imaging (PAI), and MRI. Similarly, TMPyP@MOF combined with Cy3-labeled peptides targeted cancer cells and monitored therapeutic responses, and the Zr(IV)-based porphyrinic MOF modified with upconversion nanoparticles (UCNPs) achieved an 80% cancer cell death rate under 980 nm near-infrared (NIR) light. Despite current limitations such as low selectivity and dependence on oxygen-rich environments, advancements like inner light-integrated systems (e.g., Lu@CoTCPP(Pd)) and hypoxia-resistant platforms continue to enhance the clinical potential of MOF-based photoresponsive cancer therapies [44].

The use of appropriate modifications to metal-organic frameworks (MOFs) with other materials has proven effective in overcoming their limitations while leveraging their strengths. For instance, Chen et al. synthesized Zr-UiO-66/Py-PGA-PEG-F3 for positron emission tomography (PET) imaging of tumors, demonstrating superior penetration and sensitivity compared to optical imaging [45]. This nanoplatform showed pH-sensitive drug release, with optimal release conditions observed in the tumor environment, achieving a cumulative release rate of 37.06% over two weeks. In vitro and in vivo experiments confirmed its potential for cancer radiotherapy with no observed toxicity. Deng et al. developed a core-shell nanoparticle (UCNPs@MOF NCs) functionalized with an AS1411 aptamer, which specifically targets nucleolin on cancer cells. The platform utilized UCNPs for optical imaging and achieved greater penetration with minimized light damage. It also exhibited pH-sensitive drug release, demonstrating its potential in targeted therapy, especially in cancer cells like MCF-7. Additionally, multi-functional combinations of UCNPs with MOFs, such as UCNPs@ZIF-8/FA/5-FU and UCNP@UIO-66(NH2)/FA/DOX, showed promising drug delivery and cancer treatment results. These studies underline the importance of combining various materials, like UCNPs and MOFs, to improve the efficiency of cancer therapies. However, further research is needed to refine these strategies and ensure their safe application in clinical settings [46, 47].

V. Challenges of MOFs in Cancer Therapy

MOFs offer great promise for anticancer drug delivery, but several challenges need to be addressed for their clinical application. Ensuring the stability and controllable release of MOFs in biological environments is a major hurdle, as factors like pH, temperature, and enzymatic activity can cause premature degradation and unwanted drug release. Additionally, achieving selective targeting of cancer cells while minimizing non-specific interactions with healthy tissues remains difficult. Strategies like functionalizing MOFs with targeting ligands or biocompatible coatings may help, but risks of immune clearance and long-term safety still need to be evaluated. Moreover, understanding the potential toxicity of MOFs and

their long-term behavior in the body is crucial, as they may cause unintended side effects such as inflammation or organ damage. Another challenge lies in the scalability of MOF synthesis and their translation into clinical use. While MOFs show great promise in laboratory settings, scaling up their production and maintaining consistent quality and efficacy remains a complex challenge. Variations in synthesis processes could affect drug loading capacity, release rates, and overall therapeutic effectiveness. To make MOFs viable for clinical use, strategies for scalable production, quality control, and regulatory standards must be developed [25, 44]

VI. Conclusions

Cancer is a leading cause of death in the 21st century, resulting from the uncontrolled growth of cells that disrupt normal organ function. MOFs represent a groundbreaking advancement in the field of cancer therapy, offering a promising alternative to traditional treatment methods. The unique properties of MOFs, such as their high surface area, tunable structure, and ability to encapsulate a wide variety of therapeutic agents, make them ideal candidates for improving the precision and effectiveness of drug delivery in cancer treatment. Through their potential for selective targeting, MOFs can ensure that the delivered drugs directly attack cancer cells, thereby minimizing damage to healthy tissues and reducing the harmful side effects typically associated with chemotherapy. This capability of targeted drug delivery makes MOFs a highly attractive option for enhancing cancer treatment outcomes while improving patient quality of life.

Despite their tremendous potential, several challenges must be addressed before MOFs can be fully integrated into clinical cancer therapy. Key concerns include ensuring the biocompatibility, long-term stability, and controlled release of drugs within the complex biological environment. Additionally, scalability issues related to the synthesis of MOFs and potential toxicity need to be thoroughly evaluated to ensure patient safety and the effectiveness of these treatments. Overcoming these challenges will be crucial for realizing the full clinical potential of MOF-based drug delivery systems. With continued research, optimization, and innovation, MOFs have the potential to revolutionize cancer therapy, offering safer, more effective, and less toxic alternatives to current treatment strategies. Their future integration into clinical settings could mark a significant milestone in the fight against cancer.

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