Biomimetic functionalized metal organic frameworks as multifunctional agents: Paving the way for cancer vaccine advances

Bushra Tousian [a], Ali Reza Khosravi [a,*], Mohammad Hadi Ghasemi [b], Majid Kadkhodaie [c]

[a] *Department of Microbiology and Immunology, Veterinary Medicine Faculty, University of Tehran, PO Box 1419963111, Tehran, Iran*
[b] *Applied Chemistry Research Group, ACECR-Tehran Organization, PO Box 13145-186, Tehran, Iran*
[c] *Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran*

A R T I C L E   I N F O

A B S T R A C T

Biomimetic functionalized metal-organic frameworks (Fn-MOFs) represent a cutting-edge approach in the realm of cancer vaccines. These multifunctional agents, inspired by biological systems, offer unprecedented opportunities for the development of next-generation cancer vaccines. The vast surface area, tunable pore size, and diverse chemistry of MOFs provide a versatile scaffold for the encapsulation and protection of antigenic components, crucial for vaccine stability and delivery. This work delves into the innovative design and application of Fn-MOFs, highlighting their role as carriers for immune enhancement and their potential to revolutionize vaccine delivery. By mimicking natural processes, Fn-MOFs, with their ability to be functionalized with a myriad of chemical and biological entities, exhibit superior biocompatibility and stimuli-responsive behavior and facilitate targeted delivery to tumor sites. This review encapsulates the latest advancements in Fn-MOF technology, from their synthesis and surface modification to their integration into stimuli-responsive and combination therapies. It underscores the significance of biomimetic approaches in overcoming current challenges in cancer vaccine development, such as antigen stability and immune evasion. By leveraging the biomimetic nature of Fn-MOFs, this work paves the way for innovative strategies in cancer vaccines, aiming to induce potent and long-lasting immune responses against malignancies.

1. Introduction

Vaccines are immunological preparations that often use pathogenic microorganisms that have been intentionally weakened or inactivated, or disease-related metabolites and indicators. Infections, malignancies, and other noninfectious disorders may all be prevented and controlled with their help [1–7].Vaccination will be an effective method of immunotherapy for many illnesses in the coming years. The creation of novel and high-efficiency vaccines has recently emerged as a popular and intriguing issue, with the goal of enhancing the immunogenicity of antigen and inducing long-lasting immunity and preservation. While developing innovative and highly efficient vaccines, it is crucial to choose the most suitable adjuvants or carriers [8,9]. When coupled with antigen, immunological adjuvants stimulate the body's defenses. Strong immune system activation, including induction of antigen-specific type 1 and type 2 immunological responses, may improve protection and prolong immunity [10]. The first human-approved adjuvant, alum, may increase antigen-specific antibody titer and hence stimulate humoral

immunity. Yet, it does not stimulate the immune system's cells enough. While several adjuvants have been created since then to boost both humoral and cellular immunity, only a select number have been licensed for use in humans [11,12]. New vaccines have been developed against a wide range of illnesses, thanks to the fast progress of contemporary biotechnology, however they have issues including limited immunogenicity and simple hydrolysis. These obstacles have been surmounted via the use of delivery carriers in vaccines, therefore research into the impact of carriers on the immune system has received a lot of attention [13,14]. By regulating carrier release at target tissues, antigen-loaded carriers prolong immune system activation in comparison to bare antigen. A potential technique for generating novel and incredibly effective vaccines is to use formulations of antigen and adjuvant mixed with carrier to generate a greater immune reaction compared to the absence of cargo [15–17].

Metal organic frameworks (MOFs) are the most prominent members of inorganic-organic composite materials because they are made up of numerous metal ions or metal groups and organic linking compounds

---

[18]. The adaptable nature of MOFs has made them a popular research subject. However, the primary motivation for studying MOFs is that they are better for a wide range of beneficial uses, including catalysis [19], gas storage, and separation as well as updated medication delivery systems because of their adaptable makeup and high and consistent porosity [20]. The organic/inorganic character of MOFs and the reduction in MOF size to the nano-MOF have enabled them to find a wide range of biological uses. Additionally, surface modification can change the properties of biomaterials in order to improve their application so that functionalization of the organic linkage or strut during or after production also greatly improves these MOFs' metabolic characteristics and targeting immune cells [21,22]. These include reducing cytotoxicity, increasing colloidal stability, facilitating appropriate degradation levels, and facilitating efficient cellular absorption. The MOFs have the proper characteristics to be viable candidates for biological uses, especially compared to the traditional nanocarriers (like synthetic zeolites and silica nanoparticles and organic nanocarriers like lipids and polymers) [23,24]. To begin, MOFs can be made with components that are safe and have a manageable metabolic profile. Moreover, MOFs' adaptable structures give them a wide range of shapes, compounds, diameters, and molecular characteristics, enabling them to perform a wide range of functions, including targeting lymph nodes and codelivery of antigens and immunomodulators, with the ability to carry more cytokine, adjuvant, and antigen than either liposomes or micelles. Furthermore, the ideal drug delivery system will have a high fill capacity and excellent biological preservation qualities due to the combination of a high surface area and a low pore volume. A simple search on lens databases about use of MOFs in vaccine with different keywords showed us some interesting results that we have displayed in Fig. 1. This appears to be a histogram showing the number of documents published over time, categorized by document type. The x-axis represents the publication date ranging from 1980 to 2020, while the y-axis shows the document count. The most noticeable trend is the significant increase in the number of journal articles published, particularly from around the early 2000s onwards, with a sharp rise in recent years.

Other document types like book chapters, dissertations, editorials, preprints, and news articles also show an upward trend over time, but journal articles dominate the distribution (Fig. 1a). This line chart focuses specifically on the trend for journal articles from 2014 to 2024 (projected). It shows a consistent and steep upward linear trend in the number of journal articles published each year related to the topic of interest. The search and statistical methods used here likely involved querying academic databases and literature repositories using relevant keywords to identify and count the number of publications by type and year. The resulting data was then visualized as a histogram (Fig. 1a) and line chart (Fig. 1b) to illustrate the publication trends over time. These visuals effectively highlight the increasing research interest and scholarly output in the field, especially the remarkable growth in journal article publications in recent years and the projected continuation of this trend.

The advantages of MOFs for drug transport were analyzed in depth by Wolfgang and his colleagues in contrast to mesoporous silica and dendrimers [25]. Zeolitic imidazolate frameworks' (ZIFs) defensive qualities to those of artificial nanoparticles such as $CaCO_3$ and mesoporous silica was also performed by the Falcaro group [26]. They subjected the three platforms to severe circumstances after encapsulating the HRP enzyme and then tracked the enclosed enzyme's performance. The enzymatic function was mostly preserved, and ZIF-8's better defensive qualities were evident. MOFs also demonstrated a regulated discharge of the payload in mildly acidic environments, further validating their utility as drug delivery vehicles. Eventually, MOFs offer comparatively regulated drug release because their labile metal-ligand interactions cause them to degrade only in targeted locations, such as endosomes/lysosomes or tumor cells [27–29]. The use of functionalized MOF (Fn-MOF) as transporters and adjuvants has been the subject of considerable study. This article reviews the various Fn-MOF used in
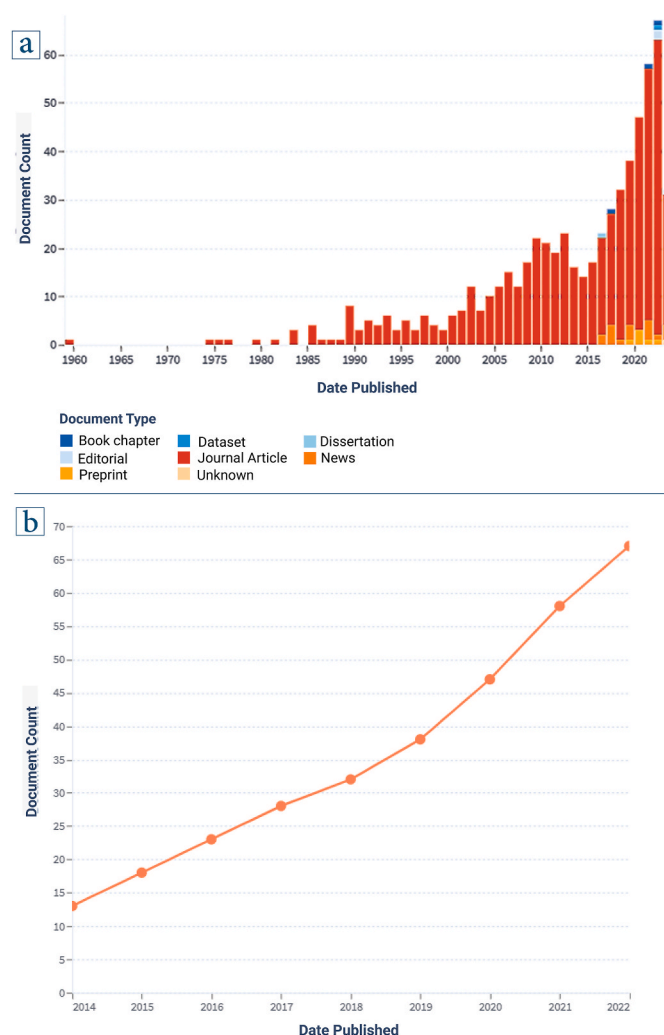
Fig. 1. History of MOFs applications in vaccine delivery (a) Detailed documents and publications about use of MOFs in vaccine over time. (b) The upward trend of articles and documents published in the last 8 years.

vaccines and the processes by which they enhance vaccine efficacy.

2. MOFs biocompatibility

If we want the whole system to be within the bioavailability range, it is crucial that the MOF compounds be biocompatible. The constructed MOFs' toxicity has been compared to that of the metals and compounds used in the process, and a clear link has been found (Fig. 2) [30]. Several other variables, such as the rates of decomposition, bio-distribution, buildup in tissues and organs, elimination from the body, functions, and the harmony between threats and advantages, also influence MOF toxicity [17,29,31–35]. Typically, MOFs for biological uses include trace amounts of important elements like iron, zinc, and magnesium.

2.1. Metal ions

Using a lethal dosage and a daily intake of metals, the most suitable cations are chosen for the production of biodegradable MOFs (Fig. 2). The median lethal dosage (LD50), or the quantity of a substance that kills half of the individuals in a community after a certain period of time, is called the lethal dose. Oral lethal dosage experiments in rats show that Ca, Mg, Fe, Zn, Ti, and Zr are suitable elements for building safe MOFs [36]. Dosage, nevertheless, varies depending on molecular composition (counter anion and oxidation state). A few metals are regarded as
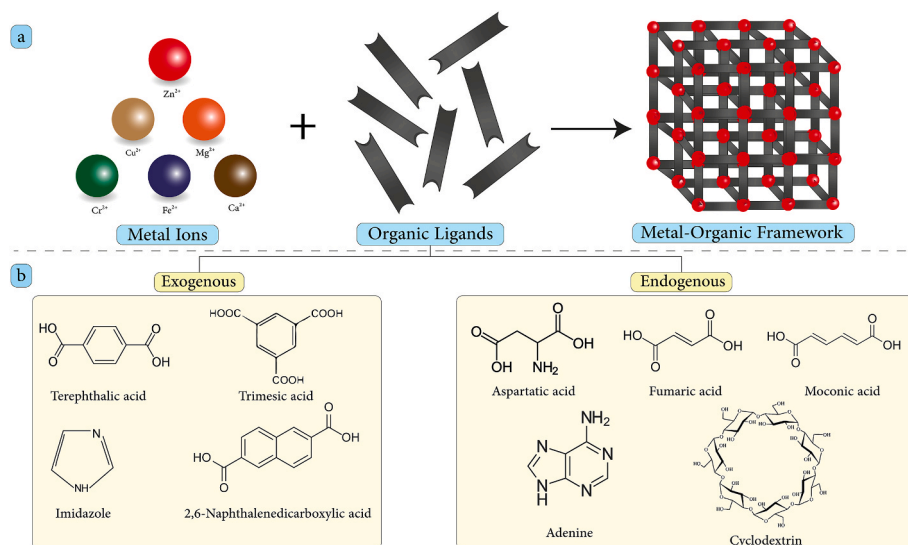
Fig. 2. The structure of MOFs. (a) An overview of the structure of MOFs as well as the placement and arrangement of ligands and metal ions in clusters and frameworks. (b) An example of some common organic ligands for MOF synthesis.

important trace elements for people and are needed in daily doses of milligrams (mg) [37]. Metals like Zr and Ti are not deemed hazardous for certain uses, such as their use in cosmetics (LD50 > 25 g/kg), because they are weakly assimilated by the body.

2.2. Ligands

Exogenous and endogenous ligands are two categories of organic ligands that may be used to build biocompatible MOFs (Fig. 2). Synthetic linkers not normally present in the body contribute to the exogenous ligands. Thus, their elimination or metabolism following in vivo administration is essential. Polycarboxylates, phosphonates, imidazolates, sulfonates, amines, pyridyl, and phenolates are all belonging to this class of compounds. Some polycarboxylates (terephthalic, trimesic, 2,6-naphthalenedicarboxylic acids) and imidazolate linkers are rather non-toxic, as shown by current biocompatibility evidence (Fig. 2) [36]. Exogenous linkers may have their ADME (absorption, delivery, metabolism, and elimination) characteristics modified by adding apolar and polar functional groups including amino, nitro, chloro, bromide, carboxylate, methyl, perfluoro, etc. [38–40]. In addition to affecting the host-guest interactions, the existence of functional groups also affects the framework's adaptability, leading to enhanced uptake as well as transportation of the cargo biomolecules [38,39]. Polycarboxylate linkers are used to adorn a wide variety of functionalized metal organic frameworks (Fn-MOFs), such as MIL-53(Fe) [41], MIL-88B(Fe) [42], UiO-66(Zr) [43], and MIL-125(Ti) [44]. Porous Zn imidazolate solids that have been organically altered are likewise suitable for inclusion within this collection [27,45–47].

2.3. Physicochemical properties

2.3.1. Size

The biodistribution, the duration of the MOFs' in vivo circulation, and their targeted effectiveness are all impacted by the particle size of the MOFs. According to the findings of the research conducted, the optimal size for this endeavor is around 200 nm [48–51]. Since there has been a lot of interest in managing the dimension of the MOFs, a broad variety of ways have been developed for accomplishing such [52]. It is not quite known how the size of the MOFs corresponds to the impact that they have on the body at this time [53]. The optimal size for nanoparticles used in tumor absorption is generally considered to be within the range of 10–100 nm. This size range allows nanoparticles to

effectively deliver drugs and achieve the enhanced permeability and retention (EPR) effect, which is crucial for cancer therapy [54]. Specifically, studies have indicated that nanoparticles with a diameter of around 50 nm may provide the best combination of deep tumor tissue penetration, efficient cancer cell internalization, and slow tumor clearance, resulting in high efficacy against both primary and metastatic tumors [55]. Zhou and his colleagues evaluated how the uptake of HeLa cells was affected by the presence of Zr-MOFs ranging in size from 30 to 190 nm [51]. This discovery showed that the uptake of the MOF PCN-224 by cells was dependent on their size. Liu et al. looked into the in vivo biodistribution of doxorubicin (DOX)-loaded MOFs (DOX@-AZIF-8), as well as their uptake into cells and their potentially fatal effects [49]. They came to the conclusion that DOX@AZIF-8 with a size of 60 nm was superior than DOX@AZIF-8 with a size of 100 nm in terms of tumor absorption as well as a longer half-life in the circulation. The biosafety features of micron- and nanoscale Mg-MOF74 (m/n-Mg-MOF74) particles were investigated and compared by Zhu's team [48]. According to the findings of the study, both micron- and nanoscale-sized Mg-MOF74 were biocompatible, however, the n-Mg-MOF74 had a wider range of permissible dosages than the micron-sized particles did. Due to the fact that an adequate dose of n-Mg-MOF74 boosted early osteogenic enhancement and angiogenesis stimulation, this finding indicates that nanoscale particles are superior to microns. The physiological characteristics of a size of 200 nm are unique [50]. The sizes of particles determine not just their velocities and dispersion throughout the body, but also their reactions to being absorbed by cancer cells, flushed out by macrophages, or both. The kidneys are also responsible for this process [56].

2.3.2. Stability

Since they are constructed using a wide variety of metal ions and organic linkers, there is a possibility that the integrity of the structure of the MOFs may be compromised when they are used for biological reasons. The structural stability of MOFs under aqueous settings is determined by a variety of characteristics, some of which include the metal-ligand bond power, the fundamental composition of the ligand, the oxidation state of the metal center and, the coordination number, as well as the size of the framework [57]. Catenation or interpenetration inside the framework, as well as the use of a linker with a higher pKa value, are all potential ways to further improve the MOFs' already impressive level of stability [58]. Because of fluctuations in pH and the composition of biological fluids, the degradability of the framework becomes vital for

releasing the package. Regardless of this, bio-applications need a particular degree of chemical stability for reaching the target locations. MOF-5 and MOF-177, which are both based on zinc and poly-carboxylate ions, are not water-stable and degrade quickly [59,60].

2.4. Synthesis of MOFs

The synthesis and tailoring of MOFs are critical processes that determine the final structure and functionality of the material. During synthesis, factors such as the choice of metal ions, organic ligands, solvents, and reaction conditions must be carefully controlled to achieve the desired crystallinity and porosity [61]. Tailoring MOFs involves modifying their structure or functionality after synthesis, which can include the introduction of defects, post-synthetic modification, or the incorporation of functional groups to enhance their properties, such as increasing stability or improving performance in specific applications [62,63].

The synthesis of MOFs may be accomplished using various methods, including nanoscale precipitation, solvothermal reactions, reverse microemulsions, and surfactant-templated solvothermal processes [64]. Nanoscale precipitation is frequently used to produce amorphous organized materials [36]. Solvothermal synthesis is conducted in a non-aqueous solvent, allowing for the use of a wide range of organic solvents that can influence the properties of the resulting MOFs, and is typically performed at higher temperatures compared to hydrothermal synthesis [65]. Hydrothermal synthesis uses water as the solvent, is generally conducted at lower temperatures, and often results in MOFs with high crystallinity and well-defined structures [65]. Surfactant-templated solvothermal synthesis uses surfactants to control the dimensions and morphologies of the nanoparticles produced, with surfactants like poly(vinylpyrrolidone) (PVP K30) acting as templates for MOF synthesis [66,67]. Reverse microemulsion involves stabilizing water droplets inside a non-polar organic phase, using a soft chemistry approach for MOF synthesis [68,69].

Table 1 summarizes the key features of these synthesis methods. Other techniques like ligand exchange and top-down synthesis can also produce MOFs with specific characteristics [70–72]. By carefully controlling the synthesis and tailoring processes, researchers can obtain MOFs with desired crystallinity, porosity, and functionalities for various applications.

2.5. Surface modification of MOFs

The change in organic ligands can significantly affect the shape and size of nanoparticles (NPs). This is because ligands are responsible for controlling the growth of NPs during synthesis. They can bind to the surface of the NPs, influencing their nucleation and growth rates. Strong metal-ligand bonds can lead to well-defined sizes and shapes, as the ligands can effectively control the crystal growth. Conversely, weakly bound ligands may desorb rapidly, leading to less control over the NP morphology [75]. The diameter and morphology of NPs can be finely tuned by adjusting the organic ligands used in their synthesis. Organic ligands play a crucial role in controlling the nucleation and growth kinetics of NPs, which in turn affects their size distribution and shape [76]. During the synthesis process, ligands can bind to the surface of the NPs, influencing the growth rates of different crystal facets. This selective

binding can lead to the formation of NPs with specific shapes, such as rods, cubes, or spheres. The strength of the ligand-metal interactions is also a determining factor; stronger binding ligands can lead to slower growth rates and smaller particle sizes, while weaker binding ligands may result in larger NPs due to faster growth rates [77]. Moreover, the molecular structure of the ligands can significantly influence the particle size. For instance, ligands with multi-functional groups or shorter hydrocarbon chains can favor smaller particle distributions compared to ligands with long hydrocarbon chains [77]. Additionally, the ratio of different ligands used can affect the morphology of the NPs; for example, using a mixture of short and long-chain ligands can result in elongated or branched structures [78]. Stabilizers play a crucial role in maintaining the NP size and chemical structures by preventing aggregation and growth, which can lead to changes in size and loss of function. They can provide steric or electrostatic stabilization, creating a barrier around the NPs that prevents them from coming close enough to aggregate. Stabilizers can also interact with the surface of NPs to maintain their dispersibility and stability in various environments [79]. Thus, to fulfill the bio-adhesive and targeting properties, it is necessary to have an appropriate design for the MOF system. For the synthesis of Fn-MOFs, two primary approaches have been employed in sources (Fig. 3) [80,81]. In the first method, the MOF is synthesized through the reaction of metal ions and ligands. Following this, organic ligands are functionalized to obtain Fn-MOFs. In the second method, the desired ligand is initially functionalized to create a functionalized ligand (Fn-ligands), which subsequently reacts with metal ions in an autoclave to produce Fn-MOFs. Due to the susceptibility of biocompounds and biomaterials to harsh conditions and temperature, the second method is not recommended for the synthesis of Fn-MOFs. This is because it necessitates the use of MOFs with biomaterials in an autoclave at high temperature and pressure, which results in the decomposition of biomaterials. However, in the first method, MOFs are produced under challenging conditions and in the second method, they are activated under less severe conditions.

Additional biophysical features of MOFs that affect their interaction with components of the physiological media, such as proteins, lipids, ions, and furthermore, include the surface's hydrophilicity as well as the type and density of the ligands that are present at the surface of the MOF. These factors are in addition to the dimensions and stability of the MOF. It is possible to adjust the outer surface of MOFs to bring about changes in both their stability and their propensity to circulate in the bloodstream until the successful targeted delivery. The most common strategy for modifying the surface properties of MOFs involves post-synthetic modification, such as covering the surface with a functional layer after the material has been synthesized. Surface modifiers for MOFs have been characterized as using a variety of different materials, including organic polymers, silica shells, and lipid bilayers. Many groups have demonstrated that silica, when used as a covering material for MOFs, promotes biocompatibility by enhancing water dispersibility and lowering the breakdown of MOFs [82–84]. The silica shell acts as a protective barrier that shields the MOF from environmental factors such as moisture, which can lead to the breakdown of the MOF structure [85]. This is particularly important for MOFs that are sensitive to water or other solvents, as the silica coating can prevent the penetration of these molecules into the MOF, thereby preserving its crystalline structure and porosity [86]. The process of coating MOFs with silica often involves the

Table 1
The key features of MOFs synthesis methods.

Synthesis Method	Solvent	Temperature	Product	References
Nanoscale Precipitation	Varies	Ambient	Amorphous	[36]
Solvothermal	Non-aqueous	High	Crystalline	[65,73]
Hydrothermal	Water	Low	Highly Crystalline	[65,74]
Surfactant-Templated Solvothermal	Non-aqueous + Surfactants	High	Controlled Morphology	[42,66]
Reverse Microemulsion	Non-polar Organic + Water Droplets	Ambient	Soft Chemistry Approach	[68,69]
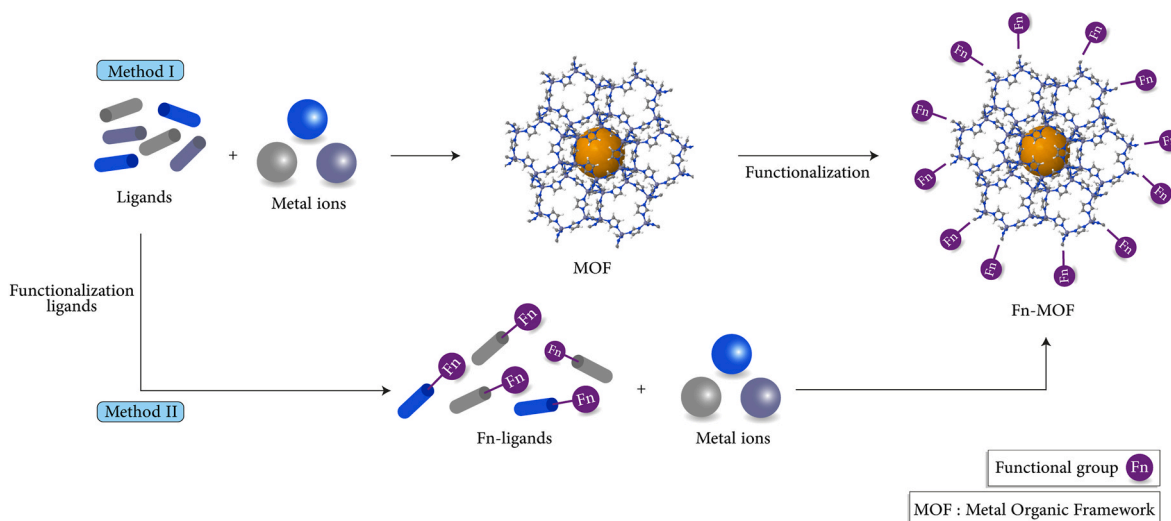
Fig. 3. Different methods of MOFs functionalization. Method 1 involved the formation of MOF followed by post-functionalization, whereas in Method 2, the initial step was the functionalization of ligands before the production of Fn-MOF.

use of a sol-gel method, where a silica precursor is hydrolyzed and condensed to form a silica network around the MOF particles. This method can be fine-tuned to control the thickness and porosity of the silica shell, allowing for the creation of a tailored protective layer that maintains the accessibility of the MOF's pores while providing stability against chemical degradation [85]. Furthermore, the silica shell can be functionalized with various organic or inorganic groups to introduce additional properties, such as enhanced biocompatibility or targeted delivery capabilities, making silica-coated MOFs versatile candidates for applications in drug delivery, catalysis, and sensing [85]. In this approach, MOF is often coated with a polymer layer first, such as polyvinyl pyrrolidone (PVP) or polyacrylic acid (PAA), which provides a base for the subsequent silica layer coating achieved by the reaction of tetraethylorthosilicate (TEOS) with basic ethanol. The silica layer thickness that is coated on the MOFs is determined by the length of time that the reaction is allowed to continue as well as the concentration of TEOS. In order to develop a dual-responsive ZIF-8 nanoscale drug delivery system, H.-L. Zhu made use of organosilica shells equipped with redox-responsive bridges of disulfide [22]. Plasma disulfide bonds are stable; however, they will break down under the influence of large quantities of glutathione (GSH), enabling their breakdown to be managed. Following the internalization process into cancer cells, endogenous GSH dissolves the disulfide bonds of the nanocarriers, therefore releasing the anti-cancer drug encapsulated in DOX. According to the results of in vivo studies, ZDOS NPs exhibited a low propensity for hemolysis and a much stronger anticancer activity than free DOX.

Polymers may be used to modify MOFs, which is another key technique. Polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), polyacrylic acid (PAA), and hyaluronic acid (HA) are the four surface-altering elements that are applied most often. Since PEG is amphiphilic, the formation of hydrogen bonds between it and MOFs results in a rise in the latter's hydrophilicity. PEGylation inhibits accumulation, opsonization of blood proteins, and absorption of MOF by immune system macrophages, hence extending the time that MOF circulates in vivo. Forgan and colleagues performed a relatively gentle conjugation of PEG to UiO-66 nanoparticles [21]. The process of PEGylation applied to UiO-66 has resulted in its enhanced stability, dispersion, and favorability for cellular uptake. In phosphate mediums, Zr-MOFs degraded very fast; however, the PEGylation of UiO-66 improved both their resistance to degradation and their dispersion in aqueous media. The hydrophilic biopolymer HA has the potential to bind to cancer cells via dealings that are mediated by HA receptors. These interactions might include excessively expressed CD44 or RHAMM receptors [87]. HA is an

effective coating material for MOF surface functionalization since it is able to overcome challenges such as inadequate bio-distribution, limited tumor targeting, and substantial adverse consequences. By using supramolecular and coordination connections amongst the three building components, Yang and his colleagues were able to generate HA-functionalized MOFs, which were then able to maintain their stability in physiological conditions. An additional important modification is the covering of MOFs with liposomes [88]. MOFs with a lipid bilayer coating have the potential to store color molecules in the porous scaffold they provide. The transformation of MOF liposomes is driven by both electrostatic and hydrophobic interactions. Colloidal resilience was enhanced, as was cancer cell absorption, thanks to MIL-100(Fe) nanoparticles that had a lipid bilayer coating [89]. Nanoparticles were not released from the cell via the intracellular pathway. The exosomes were used by the Engelke group to coat MIL-88A [90]. The use of exosomes and extracellular vesicles found in human fluids as a coating offers a number of benefits over the use of manufactured lipid covering. MOFs that have been coated with exosomes may provide longer-lasting protection from the immune system.

To generate laser or light-responsive drug delivery nanoparticles, an emulsion approach was applied. These nanoparticles had a redox-responsive selenium (Se) substituted polymer shell and a photosensitive porphyrin zirconium MOF (PCN-224 MOF) core. Both of these components were encased in a polymer shell [91]. The anticancer drug DOX was encapsulated inside nanoparticles made of poly (DH-Se/-PEG/PPG urethane) @MOF. Both chemotherapeutic agents and photodynamic treatment are capable of cleaving the poly (DH-Se/PEG/PPG urethane) polymer chain and freeing the DOX that was previously contained. The Alyami research group created a cancer cell membrane coating-based surface enhancement for the purpose of increasing nanoparticle absorption. This modification carries the antigenic properties of the source cells and has the potential to be employed in the treatment of cancer as well as for vaccination purposes. The coating of CC-ZIFs with cancer cell membranes serves the purpose of facilitating gene editing that is particular to tumor cells [35].

Ionic liquids (ILs) are a type of molten salts that are comprised entirely of weakly coordinated ions and exist in a liquid state at temperatures below 100 °C, as noted in Ref. [92]. ILs are known to possess physicochemical properties that can be modified based on specific requirements, and they have been extensively studied for various applications such as synthesis, catalysis, and electrolytes. In recent times, researchers have explored the possibility of combining ILs with MOFs to create hybrid materials that offer unique functionalities [93–96]. MOFs,

which consist of charged metal clusters, can interact electrostatically with oppositely charged ILs, and as a result, the IL species can be grafted into the MOF pores. This process can lead to the development of new functionalities and can alter properties such as the charge of the pore surface.

They are appealing for a variety of applications, including drug delivery [97], due to the fact that they offer distinctive characteristics such as low volatility, high thermal stability, and strong solvation ability. It is possible to perform surface modification of MOFs with ionic liquids using a variety of strategies, including post-synthetic modification, in situ synthesis, and solvent-assisted procedures [98]. The aforementioned techniques make it possible to incorporate ILs into the surface of the MOF, which, as a consequence, produces a hybrid material with enhanced capabilities for drug delivery.

Functionalizing ILs allows for MOF platforms that can both safeguard antigens and optimize their loading capacity. For instance, the utilization of electrostatic interactions between antigens and oppositely charged ILs can facilitate the efficient loading of antigens into MOFs. Lu et al. capitalized on this phenomenon to load substantial amounts of the model antigen ovalbumin into IL-MOFs while simultaneously preserving its structure [99]. An additional and noteworthy benefit of employing MOFs functionalized with IL for the purpose of antigen delivery is the accomplishment of a protracted release. It is a common occurrence for numerous vaccines to necessitate multiple doses, which in turn diminishes the adherence of the patient to the treatment regimen. IL-MOFs, on the other hand, enable the regulation of the rate of release of antigenic cargo from a span of hours to weeks through the modulation of IL content and chemistry [100]. Furthermore, in conjunction with the delivery of antigens, MOFs functionalized with IL have the capability to co-deliver vaccine adjuvants and immunomodulators for the purpose of amplifying efficacy. Adjuvants are substances that stimulate the immune response to an antigen, but when administered alone they often suffer from toxic effects [101].

When compared to the original MOF, the MOF that had been changed demonstrated a regulated drug release mechanism as well as better cytotoxicity against cancer cells. A further illustration of this may be seen in the work done [102], in which an ionic liquid (1-ethyl-3--methylimidazolium acetate, [EMIM][OAc]) was used to functionalize a copper-based MOF called HKUST-1. Ibuprofen, an anti-inflammatory medication, was released in a regulated manner from the IL-modified MOF, which also exhibited increased drug loading capacity and greater stability. In addition, the research showed that IL-modified MOFs have the potential to be used for targeted medication administration by affixing a targeting ligand to the surface of the MOF.

Modifying the surface of using ionic liquids for the purpose to improve the characteristics of MOFs for use in drug delivery applications is a method that shows a lot of promise. MOFs may have their stability, biocompatibility, and drug loading capacity improved by the use of this approach, which makes them more suited for deployment in vaccine and drug delivery systems.

3. Applications of Fn-MOFs in immunotherapy

In the realm of nanomedicine, the controlled release of therapeutic agents from NPs is a pivotal mechanism that ensures the precise delivery of drugs to targeted sites within the body. This controlled release is governed by several mechanisms, which include the desorption of surface-adsorbed drugs, diffusion through the NP matrix, diffusion through polymeric membrane shells in the case of nanocapsules, and polymer degradation and erosion [103–105]. By functionalizing NP surfaces with ligands that enhance drug binding, suppress immune responses, or provide targeting and controlled release capabilities, both greater efficacy and lower toxicity are achieved [106,107].

In the context of immunotherapy, NPs have been engineered to provoke immune responses against tumors while avoiding systemic side effects. For instance, immunostimulatory prodrugs inactive drugs that require activation in the body have been designed with optimized activation kinetics to stimulate the immune system to attack tumors without the side effects that occur when the active form of the drug is given intravenously [108]. These prodrugs, often structured with bottlebrush-like configurations, have shown significant reduction in tumor growth in preclinical models.

Furthermore, NPs serve as smart carriers for cancer antigens and adjuvants, improving the delivery and presentation of these molecules to the immune system, thereby potentiating the efficacy of cancer immunotherapy [109]. The emergence of nano-drug delivery systems (NDDS) encapsulating drug carriers in NPs has been shown to precisely target the tumor site with high stability and biocompatibility, prolonging the drug cycle of action and greatly reducing the occurrence of toxic side effects [110].

In recent years, MOFs have gained attention as a potentially useful platform for drug delivery owing to their many desirable characteristics. These include a large surface area, a pore size that can be adjusted, and the capacity to encapsulate and controlled release a variety of therapeutic chemicals. The intricate interplay between MOFs and biomacromolecules or drugs is a cornerstone of their utility in biomedical applications. The high pore volume of MOFs is not merely a passive space but an active site for complex interactions that govern the loading, stability, and release of therapeutic agents. The vast surface area of MOFs presents a landscape ripe for the physical adsorption of biomacromolecules and drugs. This process is governed by noncovalent interactions, including van der Waals forces, π-π stacking, hydrogen bonding, and electrostatic interactions [111]. These forces facilitate the adsorption of molecules onto the MOF surface, allowing for a reversible association that is ideal for applications where controlled release is desired. MOFs can act as protective vessels, encapsulating biomacromolecules or drugs within their cavities. This encapsulation is akin to a lock-and-key mechanism, where the size and shape of the pores dictate the specificity of the guest molecules they can host. The porous structure of MOFs provides a stable microenvironment that shields the encapsulated molecules from external degradative factors, thereby enhancing their stability and prolonging their activity [112]. Moreover, the modifiable nature of MOFs allows for the covalent attachment of biomacromolecules or drugs to their frameworks. This robust binding is achieved through post-synthetic modifications that introduce reactive functional groups capable of forming covalent bonds with guest molecules. Such a strong association ensures a stable loading of therapeutics and prevents premature release, making it suitable for long-term applications [113]. Furthermore, the metal nodes within MOFs offer sites for coordination binding, where drugs can form coordinate covalent bonds with the metal ions. This type of interaction is particularly strong and lends itself to high loading capacities. Coordination binding is a versatile mechanism that can be exploited to tailor the release profiles of drugs, making it a valuable strategy for precision medicine [114]. Additionally, MOFs have emerged as a novel strategy for the delivery of insoluble drugs in an amorphous form. By preventing the crystallization of drugs, MOFs enhance the solubility and bioavailability of therapeutics that are otherwise limited by their poor water solubility. This mechanism opens new avenues for the delivery of a wide range of drugs that require solubility enhancement for effective therapy [115]. These mechanisms collectively contribute to the multifaceted role of MOFs in drug delivery and biomacromolecule interactions. The ability to fine-tune these interactions through the careful design of MOF structures and surface functionalities underscores the potential of MOFs as versatile platforms in the realm of targeted therapy and precision medicine.

MOFs have been investigated as a vaccine delivery method in recent years because of their potential to increase vaccination effectiveness and durability (Fig. 4) (Table 2). The biomimetic mineralization of live-viral vaccines using MOFs to extend their storage stability from days to months was described [23], demonstrating one way in which MOFs are being employed for vaccine delivery. By encapsulating the vaccinations with ZIF-8 and other MOFs, the researchers were able to increase their
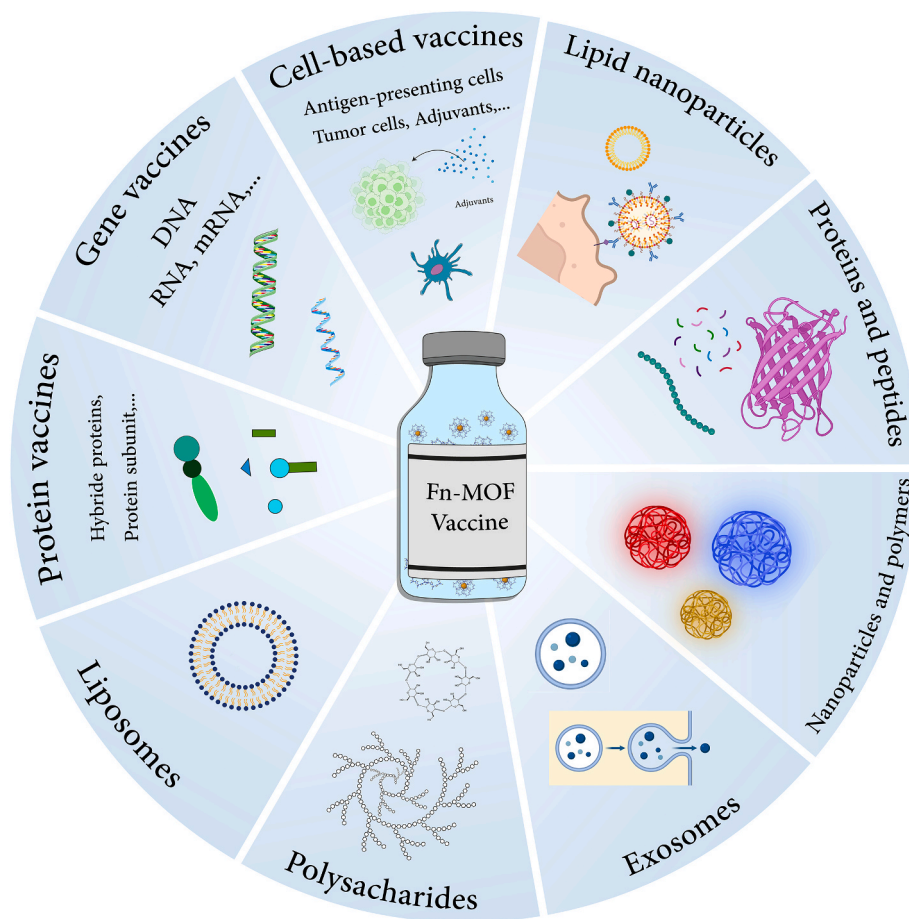
Fig. 4. Applications of Fn-MOF vaccine.

stability and maintain the vaccines' effectiveness. Pena et al. [116] conducted research on the potential of metal-organic coordination polymers for the delivery of immunomodulatory drugs, as well as vaccines for infectious diseases and cancers. The study's authors showed that MOFs may be utilized to encapsulate and transport various therapeutic substances, such as vaccinations, to specific cell types and regions. Ringaci et al. [117] employed MOFs to transport an influenza-specific DNA vaccination. Researchers boosted immune responses and protection against the virus in animal models after encapsulating the DNA vaccine in a MOF termed MIL-101. Li et al. [118] conducted a study wherein they utilized MOFs as a safeguarding layer for biomacromolecules in vaccine delivery. By adopting a biomimetic mineralization technique, the researchers were able to cultivate MOFs around the biomacromolecules, ultimately enhancing their stability and shielding them against degradation.

The use of Fn-MOFs as a delivery mechanism for cancer vaccines is one promising approach. MOFs are porous materials that can be created to have certain qualities, notably large surface area and adjustable pore size. MOFs are made up of metal ions and organic ligands, and they may be built to have specific properties. Researchers are able to design a tailored delivery system that can improve the immune response to cancer cells by functionalizing MOFs with immune-stimulating chemicals and using those Fn-MOFs. MOFs stand out in the realm of immunotherapy due to their distinctive features, which offer significant advantages over conventional materials. The tunable pore sizes of MOFs are pivotal for the encapsulation and controlled release of therapeutic agents, ensuring high encapsulation efficiency and a sustained delivery that can potentially reduce dosing frequency [114]. Their ease of functionalization allows for the attachment of various groups to enhance targeting capabilities and biocompatibility. Furthermore, the intrinsic

biodegradability of many MOFs addresses long-term toxicity concerns and negates the need for surgical removal post-therapy. The high surface area and loading capacity of MOFs facilitate a greater loading of immunomodulatory agents, which is beneficial for enhancing the immune response [114]. Lastly, the demonstrated biocompatibility of MOFs, along with their ability to evade the immune system and achieve longer circulation times, makes them ideal candidates for targeted delivery to lesion sites [119]. These collective properties underscore the potential of MOFs to serve as a multifunctional platform for the development of advanced therapeutics in immunotherapy.

Researchers have proved the potential of Fn-MOFs as a delivery mechanism for cancer vaccines. The researchers used a MOF known as MIL-101-NH2, which had the functionality added to it by a molecule described as cytosine-phosphate-guanine (CpG), which is an immune-stimulating molecule [120]. After that, the CpG-Fn-MOF was loaded with an ovalbumin-based cancer vaccine in order to protect against the disease. The researchers discovered that the CpG-Fn-MOF was able to improve the immune response to the cancer vaccination. As a consequence, the amount of tumor development that occurred in mice was significantly reduced. Dendritic cells are essential for the beginning stages of an immune response to cancer cells, and the researchers revealed that the CpG-Fn-MOF was able to target these cells successfully. The potential of MOFs as delivery systems for cancer vaccines were established in another research that was published in the journal ACS Applied Materials & Interfaces. In this particular investigation, the researchers made use of a MOF known as UiO-66. This MOF had been functionalized with a molecule known as polyethyleneimine (PEI), which is a chemical that is known to stimulate the immune system. The PEI-Fn-MOF was then loaded with a cancer vaccine called ovalbumin [121]. The researchers discovered that the PEI-Fn-MOF was able to

Table 2
Use of Fn-MOFs in drug and vaccine delivery.

MOFs	Target Disease/ Application	Highlights	References
ZIF-8	Genome editing	Targeted and cell-specific delivery of CRISPR/Cas9 machinery	[35]
ZIFs	Solid tumors	Tumor-specific targeted delivery of nivolumab	[32]
MIL-88A	Cancer, AIDS	Efficient controlled delivery of antitumoral and retroviral drugs	[29]
Mesoporous silica-MOF	E.G7-OVA tumors	PD-1 blockade monotherapy inducing tumor suppression	[118]
ZIF-8	Vaccines	Induction of robust immune memory response	[126]
UiO-66-NH2/ NO2	Osteoarthritis	Delivery system for ketoprofen	[127]
Zn-MOFs	Cancer	Anti-cancer delivery of 5-fluorouracil	[128]
ZnBDP_X	Cancer	Anti-cancer delivery of mitoxantrone	[129]
CD-MOF	Pulmonary	Pulmonary delivery of budesonide	[130]
MIL-100	HIV	Anti-HIV therapies using azidothymidine triphosphate and lamivudine triphosphate	[131]
Cu-MOFs	Cancer	Anti-tumor therapy and controlled release of ibuprofen and doxorubicin hydrochloride	[132]
UiO nano-MOFs	Ovarian cancer	Enhancing therapeutic efficacy in drug-resistant cells using cisplatin prodrug and siRNAs	[133]
MIL-101-NH2	Hepatitis B virus	Specific determination of HBV using viral aptamers	[134]
Eu3+-GMP	Cancer	Amplification of antigen cross-presentation and immunocyte mobilization for tumor elimination	[135]
Zr4+-Fe-TCPP	Cancer immunotherapy	Enhancement of M2-to-M1 macrophage repolarization by enabling intracellular accumulation of diclofenac	[136]

improve the immune response to the cancer vaccination. As a consequence, the amount of tumor development that occurred in mice was significantly reduced. The researchers also showed that the PEI-Fn-MOF has the ability to target immune cells known as dendritic cells, which are essential for the process of beginning an immune response to cancer cells. Another research discusses the potential of aptamers in the development of vaccines and Metal-Organic Frameworks (MOFs) for ovarian cancer treatment [122]. It likely explores how aptamers can be used to elicit an immune response against ovarian cancer cells by targeting VEGF. This approach could train the immune system to recognize and destroy cancer cells, offering a form of immunotherapy that is highly specific to the individual's cancer. This work might delve into how MOFs can be loaded with aptamers and drugs to create a targeted delivery system that releases medication directly to the tumor site. This could significantly increase the efficacy of the treatment while reducing side effects, as the therapeutic agents would be concentrated where they are most needed. From an innovative standpoint, combining the specificity of aptamer-based vaccines with the delivery capabilities of MOFs could lead to a groundbreaking approach in ovarian cancer treatment. Such a strategy would not only target the cancer cells more effectively but also provide a sustained release of therapeutic agents, potentially improving patient outcomes and paving the way for more advanced cancer treatments.

The study by Lei et al. presents an ultrasound-responsive metal–organic framework-based nanosystem for osteosarcoma immunotherapy [123]. This system combines sonodynamic therapy with amplified ferroptosis and IDO-blockade to induce immunogenic cell death, activating dendritic cells and triggering T-cell immune responses. It offers a new strategy for osteosarcoma treatment by synergistically inhibiting primary tumors and metastatic growth. Liu et al. discuss the nanoengineering of vaccine nanoparticles using metal–organic frameworks for tumor immunotherapy [124]. They developed a method to fabricate nanovaccines that enhance immune responses against tumors. These nanovaccines show promise in lymphoma models, inducing both innate and adaptive tumor-specific immune activation. Li et al. describe a facile approach to preparing personalized cancer vaccines using an iron-based metal organic framework [125]. Their method involves embedding antigens within the framework, resulting in high loading efficiency and effective antigen delivery. The vaccines can be tailored to different scales, enhancing antigen uptake and cytokine secretion by antigen-presenting cells. These studies represent significant advancements in cancer treatment and immunotherapy. A novel idea could be to explore the combination of these technologies to create a comprehensive treatment regimen. For instance, integrating the sonodynamic therapy from Lei et al.'s study with the nanovaccine approach of Liu et al. could potentially amplify the immune response against cancer, while the personalized vaccine platform by Li et al. could be adapted to target specific tumor antigens, offering a tailored and potent cancer therapy solution.

3.1. Fn-MOFs as vaccine adjuvants

Due to concerns about biosafety, many people are turning their focus to more costly subunit vaccinations [137]. However, a suitable adjuvant is needed when using subunit vaccinations in order to maximize immune responses and lengthen the vaccines' half-lives in vivo [138,139]. As a result, MOFs have a number of desirable qualities that make them promising adjuvants for the immune system (Fig. 5). High surface area, controllable pore size, biocompatibility, biodegradability, and a chemical toolbox for the incorporation of immune-stimulating chemicals are only some of the desirable characteristics. The ability to load and release antigens effectively and to be functionalized with immune-stimulating molecules means that MOFs may be used to boost the immune response [36]. Furthermore, MOFs can be functionalized with immune-stimulating molecules, such as adjuvants or cytokines, which are substances that enhance the immune response (Fig. 5). Adjuvants are commonly used in vaccines to improve their efficacy by activating the immune system and promoting a stronger response to the antigen. By incorporating adjuvants or other immune-stimulating molecules into MOFs, the immune response to antigens can be further enhanced [126]. Adjuvants activate and guide the immune cells to identify and respond to the antigen more effectively, thereby enhancing the immune response. Adjuvants have the capacity to activate diverse elements of the immune system, comprising antigen-presenting cells (APCs), like dendritic cells, macrophages, and B cells.

One of the fundamental mechanisms through which adjuvants magnify the immune response is by facilitating the activation and maturation of APCs [140]. The crucial role that APCs play in presenting the antigen to other immune cells, like T cells, and initiating an immune response cannot be overstated. Adjuvants can trigger the activation of APCs by means of interacting with specific receptors on their surface, thereby setting off a cascade of signaling events that culminate in the production of pro-inflammatory cytokines and chemokines. These signaling molecules are instrumental in recruiting and activating other immune cells, thereby leading to a more robust immune response (Fig. 5).

Adjuvants have the capability to promote the production of specific types of antibodies, thereby enhancing the immune response. Certain adjuvants can also induce a more balanced and diverse antibody response, including the activation of different antibody subclasses and the production of high-affinity antibodies. The significance of this is especially pronounced in vaccines that target pathogens requiring a
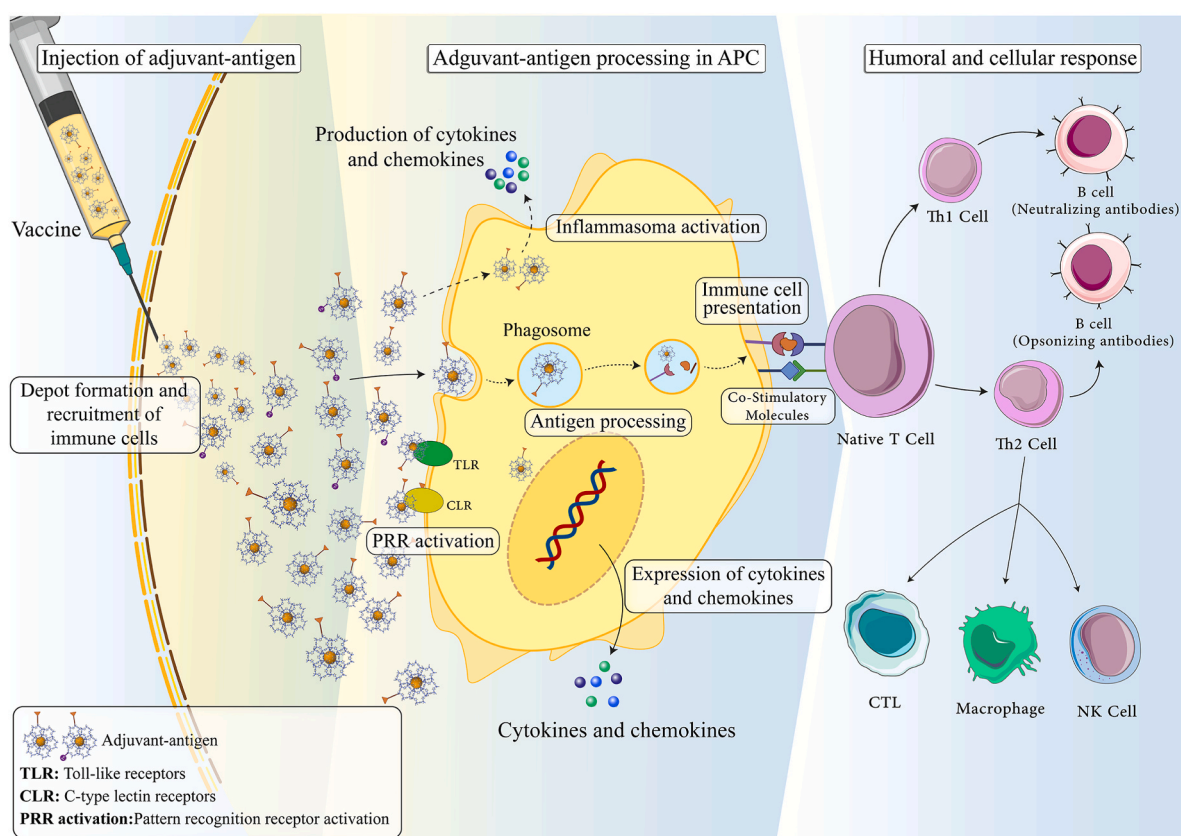
Fig. 5. Mechanisms by MOF adjuvants to enhance the immune response. (1) It is believed that certain adjuvants act as a depot at the injection site, resulting in a gradual release of antigen. (2) On the other hand, some adjuvants are associated with the temporary secretion of cytokines and chemokines. The secretion of these molecules plays a role in recruiting various immune cells to the site of injection, which in turn secrete cytokines and chemokines that further attract other immune cells to the site. These processes culminate in the development of a local immunocompetent environment at the injection site. The recruited antigen-presenting cells (APCs) express various pattern recognition receptors (PRRs) both on their surface (such as Toll-like receptors and C-type lectin receptors) and intracellularly (including nucleotide-binding oligomerization domain-like receptors and retinoic acid-inducible gene-I-like receptors). These PRRs are recognized and/or activated by the adjuvants, leading to the maturation and activation of the recruited APCs. (3) Mature APCs up-regulate the expression of major histocompatibility complex (MHC) and co-stimulatory molecules, and also exhibit an enhanced capacity for antigen processing and presentation. Subsequently, mature APCs migrate to the draining lymph nodes to interact with antigen-specific B or T cells, activating potent antibody-secreting B cell and/or effector CD8$^+$ T cell responses.

specific type of immune response for effective protection [141].

Moreover, it is noteworthy that adjuvants possess the capacity to amplify the duration of the immune response via the facilitation of memory cell creation. These memory cells are a distinct subclass of immune cells that have the ability to recall past interactions with an antigen, thereby enabling a rapid and effective reaction upon future exposure. The role of adjuvants in the generation and sustenance of a reservoir of memory cells is critical in ensuring persistent immunity against the specific pathogen [142].

A variety of adjuvants have received approval for utilization in vaccines, specifically aluminum salts (for example, aluminum hydroxide and aluminum phosphate), oil-in-water emulsions (such as MF59 and AS03), and toll-like receptor (TLR) agonists (such as monophosphoryl lipid A and CpG oligodeoxynucleotides). These adjuvants have undergone significant research and have demonstrated their capacity to increase the immune response and reinforce vaccine efficacy [143].

Recent research has shown that MOFs hold promise as immune adjuvants for use in a variety of immunotherapy settings. In order to provide a model antigen (ovalbumin) and a toll-like receptor 7/8 agonist (R848) for cancer vaccination, Zhang et al. [126] employed the MOF ZIF-8 as an adjuvant. In a mouse model of melanoma, the ZIF-8-based vaccination induced robust antigen-specific immune responses and suppressed tumor development. For the purpose of antigen administration, Singh et al. [144] synthesized a potassium and cyclodextrin MOF (CD-MOF). Immune responses were increased and the CD-MOF

showed promise as a vaccine adjuvant against infectious illnesses. This research underlines the potential use of MOFs as immune adjuvants for a wider variety of disorders.

The use of MOFs as an adjuvant for tailored immunotherapies such neoantigen-based cancer vaccines has also been investigated. Tumor-specific antigens, or neoantigens, are produced by somatic mutations in cancer cells and may be targeted by the immune system for enhanced immunotherapy. Customized MOF delivery of neoantigens and immune-stimulating compounds may improve the effectiveness of cancer vaccines developed for individual patients [145]. The researchers' Sun et al. [146] looked into the possibility of using MOFs as a means of enhancing the induction of immunogenic cell death (ICD) in cancer cells. They designed a MOF-based nanoplatform that co-delivered a chemotherapeutic drug (DOX) and an immunoadjuvant (R837) in order to improve immune cell differentiation and induce an effective immunological response. A mouse model of breast cancer was used in the research, and it was shown that a nanoplatform based on MOF was able to successfully inhibit the development of tumors and the spread of metastases.

Building on the potential of MOFs as vaccine adjuvants, the versatility of these frameworks allows for the co-delivery of antigens and adjuvants within a single particle. This is particularly advantageous for vaccines targeting complex diseases like cancer, where a strong and precise immune response is crucial. A study by Chong et al. (2024) [147] demonstrated that zirconium-based MOFs could be engineered to release antigens and adjuvants in a controlled manner, leading to

enhanced T-cell responses. This approach could be particularly beneficial for ovarian cancer, where the immune system often fails to recognize and attack cancer cells effectively. The environmental stability of MOFs also makes them suitable for use in vaccines that require transport to remote areas. Research by Desai et al. (2024) [148] showed that MOFs could maintain their structural integrity and functional properties under varying temperatures and humidity levels. This characteristic could be pivotal in the global fight against cancer, allowing vaccines to reach populations in less accessible regions without compromising efficacy and highlighting their broad-spectrum benefits and potential for next-generation vaccine development.

Furthermore, the biocompatibility and degradability of MOFs are essential for their safe use in humans. A recent review by Santos et al. (2024) highlighted the advances in the synthesis of biodegradable MOFs that can be safely metabolized by the body after delivering their payload. This reduces the risk of long-term toxicity and makes MOFs an attractive option for repeated vaccine administrations.

In a separate piece of research, Lu et al. (2022) looked at the possibility of using MOF-based nanocomposites as a kind of cancer immunotherapy. For the purpose of photodynamic therapy (PDT)-induced immunotherapy, they developed a nanocomposite that consists of a MOF called ZIF-8 and a photosensitizer called chlorin e6. By destabilizing the immunosuppressive milieu and creating an effective immune response, the MOF-based nanocomposite demonstrated outstanding anticancer and antimetastatic effects [149]. Scientists are looking towards novel methods and applications to find ways to make immunotherapies even more successful as the area of MOF-based immune adjuvants continues to develop. The following is a list of parts that cover recent advancements and new paths that are currently being investigated in this discipline. Recent research has highlighted the potential of aluminum-based MOF nanoparticles as pulmonary vaccine adjuvants [150]. These nanoparticles have been shown to activate antigen-presenting cells more effectively than traditional adjuvants like aluminum salts (alum). In particular, the study by Stillman et al. (2023) demonstrated that Al-based MOFs, such as DUT-5, elicited higher mucosal IgA antibodies and detectable IgG2a titers, indicative of a cellular immune response1. This suggests that MOFs could be a key player in enhancing mucosal immunity, which is crucial for protection against aerosolized pathogens. The clinical translation of MOFs is also gaining momentum. A commentary by Tyagi et al. (2023) discusses the progress of MOFs towards clinical applications, particularly as drug carriers and vaccine adjuvants [151]. The unique properties of MOFs, including tunable host–guest interactions and high drug loading capacity, make them ideal candidates for these applications. Despite the slow progress in clinical trials, the potential for MOFs in healthcare settings is significant, with the ability to improve the stability and delivery efficacy of loaded drugs. Furthermore, a study from MIT researchers in 2024 has shown that MOFs can provoke a strong immune response by activating the innate immune system through toll-like receptors [152]. This type of nanoparticle has been successful in encapsulating and delivering parts of the SARS-CoV-2 spike protein, acting as an adjuvant to enhance the vaccine's effectiveness [153]. The dual functionality of MOFs as both delivery vehicles and adjuvants present a promising avenue for the development of more powerful vaccines, potentially leading to more robust and long-lasting immunity against various pathogens. Huang et al. discuss the enhancement of humoral and cellular immunity through STING activation by mesoporous MOF adjuvants [154], while Ehrman et al. present a scalable synthesis method for antigen depots based on MOFs, which could significantly improve the humoral immune response [155].

In conclusion, the integration of MOFs as vaccine adjuvants represents a significant advancement in immunotherapy. Their ability to enhance the immune response and serve as effective delivery systems for antigens positions them as a transformative technology in vaccine development. These advancements represent a significant leap forward in vaccine technology. The integration of nanotechnology with immunology opens up new avenues for creating more stable, potent, and targeted vaccines. A novel idea could be the development of a universal platform that combines the specificity of MOFs with the adaptability of nanoadjuvants to create personalized vaccines. This platform could use machine learning algorithms to analyze individual immune responses and tailor vaccine components for optimal efficacy, potentially revolutionizing personalized medicine and global health. As research continues to unfold, MOFs stand to play a pivotal role in the future of vaccine science. Future studies should concentrate on finding solutions to existing problems and opening up promising new avenues in the rapidly expanding area of MOF-based immune adjuvants.

3.2. Fn-MOFs in stimuli-responsive therapies

In the context of immunotherapy applications, the use of stimuli-responsive Fn-MOFs has emerged as a potentially useful technique for producing regulated release of antigens and immune-stimulating chemicals. These MOFs have the ability to react to certain environmental triggers, such as pH, temperature, enzymes, or redox conditions, which enables them to release their cargo in a targeted and controlled manner. This strategy might increase the effectiveness and safety of immune adjuvants based on MOF by ensuring that the immune response is triggered only at the right place and time. In turn, this could improve the efficacy of MOF-based immune adjuvants.

An immune-stimulating chemical called CpG oligodeoxynucleotide and a model antigen called ovalbumin were packaged inside a pH-responsive MOF called ZIF-8 that was designed [126]. The MOF displayed pH-responsive release behavior, with an accelerated release under acidic circumstances. Acidic conditions are often present in tumor microenvironments and endosomes. This pH-responsive MOF showed promise for increasing immune response and antitumor activity in a mouse model of melanoma, which suggests that it might be used to treat the disease. An enzyme-responsive MOF known as PCN-333 was created with the purpose of facilitating the targeted administration of DOX, a chemotherapeutic drug, and R848, an immunological adjuvant. Matrix metalloproteinase-2 (MMP-2) is an enzyme that is overexpressed in the tumor microenvironment. The MOF was functionalized with a peptide substrate that could be cleaved by MMP-2. The MOF was able to release its payload after being cleaved by MMP-2, which resulted in increased immune activation and anticancer effects in a mouse model of breast cancer [156]. In the study that He et al. (2020) conducted, they used a redox-responsive MOF called MIL-100 to co-deliver DOX, which is a chemotherapeutic drug, and CpG oligodeoxynucleotide, which is an immunological adjuvant. The MOF was functionalized with disulfide bonds, and these bonds were designed to break apart when subjected to the reducing conditions that are typical of tumor cells. In a mouse model of lung cancer, this redox-responsive MOF demonstrated regulated release behavior and increased anticancer activity [157]. These investigations provide evidence that stimuli-responsive Fn-MOFs have the potential to improve the efficacy of immunotherapies by permitting the targeted and regulated release of immune-stimulating chemicals and antigens. The completion of more studies in this field could result in the invention of more sophisticated immune adjuvants based on MOFs that have enhanced safety and effectiveness characteristics.

3.3. Fn-MOFs in combination therapies

MOF-based immune adjuvants have the potential to improve the overall efficacy of therapy by targeting many components of the immune response (Fig. 6). This may be accomplished by combining them with other immunotherapies, such as immune checkpoint inhibitors or adoptive T-cell treatments. This strategy could be useful in overcoming the limits of individual medicines and improving the results for patients. Conventional cancer therapies such as radiotherapy and chemotherapy can have long-term side effects. Metal-organic frameworks (MOFs) can be used as a non-invasive alternative treatment with excellent
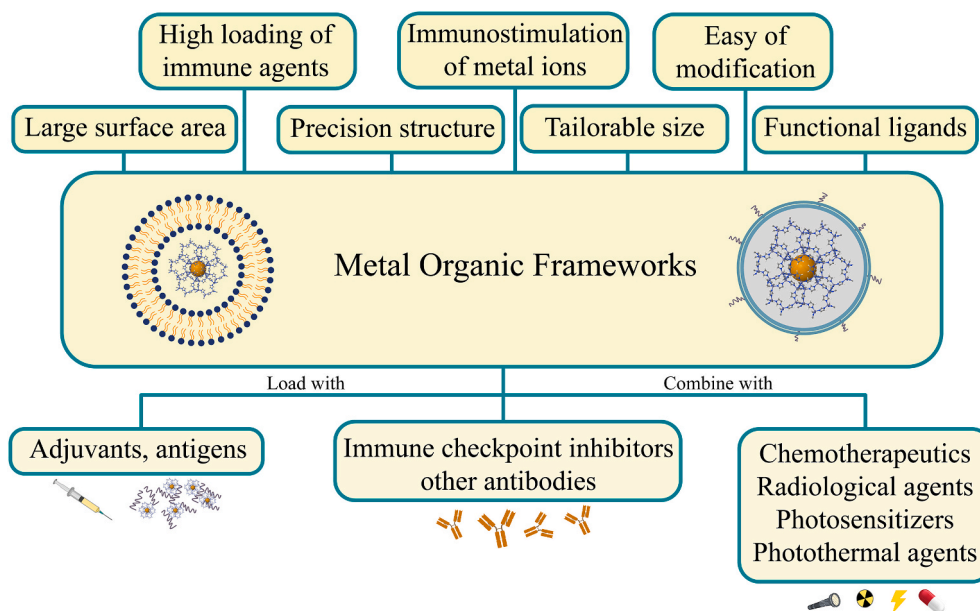
Fig. 6. Combination and multifunctional Fn-MOFs applications.

selectivity, and can promote systemic antitumoral immune responses, acting against metastasis and tumor recurrence.

Lu et al. (2020) revealed that using a MOF-based vaccination (UiO-66-NH$_2$) in conjunction with immune checkpoint blockade treatment (anti-PD-L1 antibody) resulted in synergistic anticancer benefits in a mouse model of melanoma. The MOF-based vaccination included both an immunological adjuvant in the form of CpG oligodeoxynucleotide and a tumor-associated antigen in the form of gp100. In comparison to each medication being administered independently, the combination therapy dramatically increased the activation of antigen-specific T cells and decreased the development of the tumor [118]. Zhao et al. (2023) presented a new system called GOx@MOF@Fe3+ which combined glucose oxidase (GOx) and Fe3+ loaded into a MOF [158]. The goal was to enhance chemodynamic therapy (CDT) for cancer treatment, which uses Fenton reactions to produce reactive oxygen species that can kill cancer cells. In the study conducted by Wang et al. (2019), a multifunctional MOF called PCN-224 was created with the purpose of simultaneously delivering a chemotherapeutic drug called DOX, an immunological adjuvant called R848, and a photothermal agent called indocyanine green. In response to irradiation with near-infrared light, the MOF exhibited regulated release behavior, which activated the photothermal impact and accelerated the release of the encapsulated cargo. In a mouse model of breast cancer, this multifunctional MOF showed promise for synergistic chemo-immunotherapy and photothermal therapy [159]. This was due to the increased activation of tumor-infiltrating lymphocytes. Gaowei et al. (2021) devised a combination therapy for a mouse model of lymphoma that included a MOF-based adjuvant (ZIF-8) and chimeric antigen receptor (CAR)-T cell therapy. Both an immune-stimulating substance in the form of a CpG oligodeoxynucleotide and a model antigen in the form of ovalbumin were placed onto the MOF. The use of combination therapy greatly increased the growth and activation of CAR-T cells, which ultimately led to greater antitumor effectiveness in comparison to the use of either therapy individually [160].

These findings provide evidence that the potential of multifunctional Fn-MOFs for increasing the efficiency of immunotherapies by concurrently delivering antigens, adjuvants, and other therapeutic molecules. Researchers are able to design more effective and adaptable MOF-based therapy platforms if they target numerous components of the immune response as well as the microenvironment of the tumor.

3.4. Biomimetic Fn-MOFs

Emerging as a new trend in the field of MOFs, biomimetic Fn-MOFs include the incorporation of biological components such as proteins or peptides into the MOF structure. This strategy has the potential to improve the biocompatibility, targeting ability, and functionality of MOFs for a wide range of biomedical applications, including drug delivery, biosensing, and bioimaging.

Biomimetic MOFs can be conveniently synthesized by seamlessly integrating diverse biological moieties, including but not limited to enzymes, peptide sequences, DNA, antibacterial agents, and cellular membrane components, into the MOF structure, thereby imparting them with unique and fascinating properties that have previously been unattainable [161–163]. For instance, the integration of enzymes into MOFs has paved the way for the development of innovative MOFs that can effectively mimic the functionality of catalytic antibodies. Specifically, glucose oxidase enzymes have been successfully incorporated into a MOF structure, thereby leading to the creation of a highly stable material that closely mimics the catalytic function of glucose oxidase and exhibits superior stability compared to its conventional counterparts [164]. Moreover, a recent study has demonstrated the successful integration of catalase enzymes into a MOF structure, which can closely mimic the natural antioxidant activity and effectively neutralize harmful reactive oxygen species, thereby highlighting the immense potential of biomimetic MOFs in various fields ranging from biomedicine to environmental science [165].

Peptide-functionalized metal-organic frameworks (MOFs) have been strategically crafted to imitate protein channels with the aim of facilitating selective molecular transport. MOFs that have been functionalized with short peptide sequences have exhibited the ability to replicate the size-selective transport of aquaporin water channels [166]. In a separate study, a nuclear localization sequence peptide was incorporated into a MOF creating a complex that could selectively transport gene regulation proteins into the nucleus of cells [26].

DNA-based MOFs, which are a class of crystalline materials composed of inorganic nodes and organic linkers, have been demonstrated to have the potential to perform as biosensors by transducing molecular recognition events. One example of such a biosensor is the incorporation of DNA aptamers into a MOF, which allows for the creation of a fluorescence sensor with high sensitivity and selectivity, particularly in the detection of cocaine, a notorious drug of abuse. This

biosensor exhibits promising features that can be utilized in various applications, such as drug detection and diagnostics [167]. In addition to the aforementioned example, MOFs that are functionalized with DNAzymes, which are DNA molecules with catalytic activity, have been developed as colorimetric biosensors for lead ions, offering a sensitive and selective detection method [168]. Furthermore, MOFs containing nucleic acid probes have been designed and investigated for the rapid detection of viruses such as human papillomavirus (HPV) and human immunodeficiency virus (HIV), which are responsible for causing significant morbidity and mortality worldwide. The integration of DNA-based MOFs in biosensing applications has proven to be an exciting and expanding field that holds great potential for the development of new and innovative biosensors for various applications [169].

The process of functionalization, which involves the introduction of antibacterial agents, has led to the development of MOFs with exceptional bactericidal capabilities that are reminiscent of natural antimicrobial peptides. It has been observed that the incorporation of the antibiotic ciprofloxacin into the surface coating of a MOF has resulted in the sustained release of the drug, thereby exhibiting an extended period of broad-spectrum antibacterial activity [170]. Equally noteworthy is the fact that MOFs that have been loaded with the disinfectant chlorhexidine have been shown to possess bactericidal effects and the ability to disrupt biofilm [171]. The process of coating MOFs with cellular membrane components results in a biomimetic fashion that serves to cloak the MOFs from the immune system, thereby enhancing their efficacy. For instance, MOFs coated with red blood cell membranes have been observed to have an extended circulation time and evade the immune system more effectively [29]. As an illustration, cancer cell membrane-coated MOFs have been able to mimic cancer cell homing behaviors, leading to improved drug delivery [26]. This bio-inspired stealth strategy enables MOFs to bypass immune clearance, thereby promoting their effectiveness. Moreover, biomimetic MOFs hold immense promise for enhancing vaccine and immunotherapy approaches. MOFs functionalized with immune-stimulating adjuvants and loaded with vaccine antigens can function as artificial antigen-presenting cells, thereby eliciting stronger and more targeted immune responses [126,172]. The high porosity and tunable structure of MOFs allows sustained co-delivery of adjuvants and antigens to mimic natural antigen presentation. In addition, MOFs coated with cell membrane proteins have been used to cloak antigens and prevent immune tolerance, thereby enhancing the immune response [173,174]. In the domain of cancer immunotherapy, it has been observed that MOFs adorned with tumor antigens have the potential to replicate the traits of natural tumor cells, thereby inducing a strong and efficacious anti-tumor response by the immune system upon their application as vaccines [175–177].

Recent studies have unveiled the potential of MOFs and biomimetic nanoparticles in cancer therapy, particularly in modulating the tumor microenvironment to amplify immunotherapy. For instance, Wang et al. developed a biomimetic MOF nanosystem that uses cancer cell membrane-coated ZIF-8 to deliver oxaliplatin and imiquimod, enhancing both localized antitumor immunity and systemic responses [178]. Xu et al. transformed "cold" tumors into "hot" ones, activating immune cells and targeting primary and metastatic tumors with a biomimetic nanosystem [179]. Ding et al. reviewed the advances in tumor immunotherapy mediated by immune cell-derived biomimetic MOFs, which overcome the challenges of mono-immunotherapy [180]. Song et al. reported on a bimetallic MOF-based biomimetic nanoplatform that synchronizes DNA demethylation and RNA hypermethylation to enhance anti-leukemia immunity [181]. Li et al. explored the biomedical applications of MOFs in cancer therapy, focusing on their stimuli-responsive and biomimetic properties for targeted delivery and diagnosis [182]. Tao et al. presented a biomimetic camouflaged MOF for enhanced siRNA delivery in the tumor environment, addressing the challenges of nuclease degradation and immune detection [183]. Sun et al. enhanced cell pyroptosis with biomimetic nanoparticles for melanoma chemo-immunotherapy, combining pyroptosis-inducer oxaliplatin and immunomodulator imiquimod [184]. Liu et al. developed manganese-based microcrystals with Ythdf1-targeted biomimetic nanovaccines for dendritic cell orchestration, improving the efficacy of cancer vaccines [185]. Chen et al. created a biomimetic MOF-based nano-immunoactivator that disrupts ion homeostasis for strengthened tumor microwave-immunotherapy [186]. these studies represent a significant leap forward in the field of cancer treatment. A novel idea could be the integration of these MOF-based therapies with real-time monitoring systems, such as wearable sensors, to track treatment efficacy and adjust dosages dynamically, offering a personalized and adaptive approach to cancer therapy. This could lead to more precise and effective treatments, potentially improving patient outcomes and paving the way for more advanced cancer treatments.

The functionalized MOFs possess a high degree of modularity and biomimicry capabilities, rendering them an extremely versatile and adaptable platform with the potential to replicate the intricate immune signaling mechanisms of natural cells. By doing so, they offer a promising avenue for enhancing the efficacy of next-generation vaccines and immunotherapies. The biomimetic functionalization of MOFs holds significant promise as a means of imparting bio-inspired properties and developing innovative smart materials for a wide range of applications. The continued advancement of this field could pave the way for groundbreaking breakthroughs in therapeutic delivery, point-of-care diagnostics, environmental remediation, and beyond.

3.5. Fn-MOFs as carriers for immune enhancement

Although MOFs are used as immune adjuvants, they are more commonly used as vehicles for delivery. MOFs have the potential to be used as immunoactivators or immunomodulatory carriers, meaning that they have the ability to induce immunological activation or tolerance depending on the circumstances [187]. The interaction between MOFs and immunological components may promote the formation of unique therapeutic activities, giving valuable information for the development of innovative immunotherapies. This is due to the fact that the interaction can help generate particular therapeutic actions. The transport of many kinds of biomacromolecules, such as antigens, antibodies, enzymes, therapeutic proteins, DNA/RNA, polypeptides, and polysaccharides, is one of the most important uses of MOFs in immunological boosting. MOFs are able to efficiently enter several cell types due to their high biocompatibility and low cytotoxicity [114]. Some of the cell kinds that can be effectively penetrated by MOFs include liver cells, T cells, vascular cells, lung cells, and germ cells.

When biological entities are incorporated into MOF matrices, MOF biocomposites are produced. These MOF biocomposites have functional properties that cannot be detected in the individual components, such as higher chemical and thermal stability, better biocompatibility, and increased bioactivity and they have been used in the manipulation of viruses and cells, revealing their potential for applications relating to immunological improvement [188]. MOFs are advantageous in a number of ways, but one of the most significant is their capacity to encapsulate biomolecules and shield them from degradation, therefore increasing the biomolecules' stability and bioavailability [189]. For example, MOFs have been utilized to encapsulate enzymes, which has the effect of maintaining both the enzymes' functionality and their stability even in severe circumstances [165]. This characteristic may be especially helpful for the delivery of immune-enhancing biomolecules, such as cytokines, which are often susceptible to degradation [189]. MOFs may also be functionalized with a variety of ligands that target particular immune cells, such as dendritic cells, macrophages, or T cells, and so boost the immune response [190]. This can be accomplished by targeting specific immune cells with the MOFs. A zirconium-based MOF (UiO-66) functionalized with mannose, for instance, was shown to be able to efficiently target and activate dendritic cells, which led to a powerful immunological response in research that was conducted by

Benchafia et al. [191]. Moreover, Pena et al. explore metal-organic coordination polymers for delivering immunomodulatory agents, offering insights into their application in infectious disease and cancer vaccines [192]. MOFs, because of their one-of-a-kind features, biocompatibility, and capacity to interact with immunological elements, show significant potential as carriers for immune augmentation and immunomodulation. Additional research and development in this field may result in a generation of novel immunotherapies as well as enhanced treatment choices for a variety of diseases.

4. Summary and perspectives

The development of vaccinations that are both efficient and secure is essential not only for the prevention and control of infectious diseases but also for the treatment of a variety of diseases that are not contagious, such as cancer. In recent years, researchers have been investigating various approaches to increase the effectiveness of vaccinations. These approaches include the use of novel delivery methods and immune adjuvants. Utilizing Fn-MOFs as vaccine carriers and combining them with immunological adjuvants in order to elicit a stronger immune response is an example of a strategy that shows promise. This approach has shown a great deal of promise for enhancing the effectiveness of vaccinations and delivering enhanced protection against a wide range of diseases.

As mentioned in the previous sections, MOFs are made of ions and clusters joined by organic linkers due to their large surface area, variable pore size, and diverse chemistry have the potential to be functionalized such that they may encapsulate and protect antigenic components throughout the process of vaccine generation. we discuss how solvothermal synthesis allows for fine-tuning of MOF structures by varying the solvent type, which can significantly impact the properties of the resulting MOFs [193]. In contrast, hydrothermal synthesis, typically using water as the solvent, is more environmentally friendly and can produce highly crystalline MOFs [194]. Furthermore, we have included a subsection that specifically addresses the unique contributions of our review. Our review brings forth a critical analysis of the recent advancements in the functionalization of MOFs and their implications for immunotherapy. Unlike previous reviews, we focus on the innovative strategies for enhancing the immunogenicity of antigens using MOFs and provide a forward-looking perspective on the potential of these materials in vaccine development and beyond.

This will ensure the components' stability and allow for controlled release. An essential component of this method is the use of immunological adjuvants in the production of MOF-based vaccines. Adjuvants are compounds that boost the immune response that the body has to an antigen, which ultimately results in a stronger immunity that lasts for a longer period of time. Researchers hope to achieve synergistic effects by combining MOFs and adjuvants in their study. These effects will result in an increase in the effectiveness of vaccines. MOF-based vaccine delivery system was capable of successfully encapsulating and releasing a model antigen, which resulted in a robust immunological response. As mentioned in the sections above, the effective creation of a MOF-adjuvant system that increased the immunogenicity of subunit vaccines.

Despite the encouraging findings, there are still a number of obstacles to overcome in the process of developing vaccines based on MOFs. while the literature provides a wealth of information on the synthesis and potential applications of Fn-MOFs, there is often a lack of in-depth discussion regarding the long-term stability and biodegradability of these materials. This is particularly pertinent in biomedical applications where the breakdown products of Fn-MOFs could have significant biological effects. The review would benefit from more comprehensive studies that not only assess the immediate functionality of Fn-MOFs but also their long-term behavior in biological systems. Moreover, the scalability of MOF production is a topic that is often glossed over in the literature. While many studies demonstrate the successful synthesis of MOFs on a laboratory scale, the transition to industrial-scale production poses significant challenges. These include the cost-effectiveness of the synthesis process, the availability of raw materials, and the reproducibility of the MOFs' properties on a larger scale. A more focused discussion on the economic and practical considerations of MOF manufacturing would provide valuable insights for the field. Furthermore, the immunomodulatory effects of Fn-MOFs are frequently presented without a detailed exploration of the underlying mechanisms. A deeper understanding of how Fn-MOFs interact with the immune system at the molecular level is crucial for the design of more effective immunotherapeutic agents. Studies that delve into the molecular interactions between Fn-MOFs and immune cells, as well as the subsequent cellular responses, would significantly advance our knowledge in this area. The possible toxicity of MOFs is a serious problem that has to be thoroughly examined and mitigated to guarantee the safety of vaccine formulations. In addition, more research is required to study the processes behind the improved immunogenicity of MOF-adjuvant systems and to improve the chemical composition and structure of MOFs for particular vaccine applications. These applications include optimizing the structure of MOFs for specific vaccines.

In conclusion, our critical commentary on the literature highlights the need for a more holistic approach to the study of Fn-MOFs. Future research should aim to address the gaps identified in long-term stability, scalability of production, and the immunomodulatory mechanisms of Fn-MOFs. By tackling these challenges, we can unlock the full potential of Fn-MOFs and pave the way for their successful translation from the laboratory to real-world applications. Fn-MOFs paired with immune adjuvants constitute an interesting and potentially useful technique for improved immunotherapy. This strategy has the potential to boost the effectiveness of vaccinations and make a contribution to the battle against a wide range of illnesses. The innovative approaches that we believe will be crucial in advancing the field, such as the integration of machine learning for the design of MOFs and the exploration of new ligand types that can enhance the functionality of MOFs in a biological context. However, in order to solve the problems that are involved with the creation of MOF-based vaccines and to fully realize the promise of this new technique, further research is required.

CRediT authorship contribution statement

Bushra Tousian: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ali Reza Khosravi:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Mohammad Hadi Ghasemi:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Majid Kadkhodaie:** Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] M.A. Rolfes, et al., Effects of influenza vaccination in the United States during the 2017–2018 influenza season, Clin. Infect. Dis. 69 (11) (2019) 1845–1853.

[2] A. Schuchat, et al., Progress in vaccine-preventable and respiratory infectious diseases—first 10 years of the CDC national center for immunization and respiratory diseases, 2006–2015, Emerg. Infect. Dis. 24 (7) (2018) 1178.

[3] A. Ährlund-Richter, et al., Changes in cervical human papillomavirus (HPV) prevalence at a youth clinic in Stockholm, Sweden, a decade after the introduction of the HPV vaccine, Front. Cell. Infect. Microbiol. 9 (2019) 59.

[4] B. Donaldson, et al., Multi-target chimaeric VLP as a therapeutic vaccine in a model of colorectal cancer, Journal for immunotherapy of cancer 5 (2017) 1–13.

[5] S.J. Danishefsky, Y.-K. Shue, M.N. Chang, C.-H. Wong, Development of Globo-H cancer vaccine, Acc. Chem. Res. 48 (3) (2015) 643–652.

[6] X. Chen, et al., Effectiveness and safety of a therapeutic vaccine against angiotensin II receptor type 1 in hypertensive animals, Hypertension 61 (2) (2013) 408–416.

[7] C. Grundman, Vaccination against atherosclerosis, in: Inflammation and Atherosclerosis, Springer, 2011, pp. 529–553.

[8] K.T. Mody, et al., Silica vesicles as nanocarriers and adjuvants for generating both antibody and T-cell mediated immune responses to Bovine Viral Diarrhoea Virus E2 protein, Biomaterials 35 (37) (2014) 9972–9983.

[9] C.J. Davitt, et al., Alpha-galactosylceramide enhances mucosal immunity to oral whole-cell cholera vaccines, Mucosal Immunol. 12 (4) (2019) 1055–1064.

[10] T. Hayashi, et al., DAMP-inducing adjuvant and PAMP adjuvants parallelly enhance protective type-2 and type-1 immune responses to influenza split vaccination, Front. Immunol. 9 (2018) 2619.

[11] S. Lee, M.T. Nguyen, Recent advances of vaccine adjuvants for infectious diseases, Immune network 15 (2) (2015) 51–57.

[12] G. Del Giudice, R. Rappuoli, A.M. Didierlaurent, Correlates of adjuvanticity: a review on adjuvants in licensed vaccines, in: Seminars in Immunology, Elsevier, 2018.

[13] T. Gómez Dacoba, et al., Polysaccharide Nanoparticles Can Efficiently Modulate the Immune Response against anHIV Peptide Antigen, 2019.

[14] S. Persano, et al., Lipopolyplex potentiates anti-tumor immunity of mRNA-based vaccination, Biomaterials 125 (2017) 81–89.

[15] J. Xu, et al., Nanovaccine based on a protein-delivering dendrimer for effective antigen cross-presentation and cancer immunotherapy, Biomaterials 207 (2019) 1–9.

[16] H. Liu, et al., Aluminum hydroxide colloid vaccine encapsulated in yeast shells with enhanced humoral and cellular immune responses, Biomaterials 167 (2018) 32–43.

[17] X. Zhong, et al., An aluminum adjuvant-integrated nano-MOF as antigen delivery system to induce strong humoral and cellular immune responses, J. Contr. Release 300 (2019) 81–92.

[18] S.L. James, Metal-organic frameworks, Chem. Soc. Rev. 32 (5) (2003) 276–288.

[19] K.M. Choi, K. Na, G.A. Somorjai, O.M. Yaghi, Chemical environment control and enhanced catalytic performance of platinum nanoparticles embedded in nanocrystalline metal–organic frameworks, J. Am. Chem. Soc. 137 (24) (2015) 7810–7816.

[20] J.L. Rowsell, O.M. Yaghi, Effects of functionalization, catenation, and variation of the metal oxide and organic linking units on the low-pressure hydrogen adsorption properties of metal– organic frameworks, J. Am. Chem. Soc. 128 (4) (2006) 1304–1315.

[21] I.A. Lazaro, et al., Selective surface PEGylation of UiO-66 nanoparticles for enhanced stability, cell uptake, and pH-responsive drug delivery, Chem 2 (4) (2017) 561–578.

[22] S.-Z. Ren, et al., Nanoscale metal–organic-frameworks coated by biodegradable organosilica for pH and redox dual responsive drug release and high-performance anticancer therapy, ACS Appl. Mater. Interfaces 11 (23) (2019) 20678–20688.

[23] R. Singh, et al., Biomimetic metal-organic frameworks as protective scaffolds for live-virus encapsulation and vaccine stabilization, Acta Biomater. 142 (2022) 320–331.

[24] X. Liao, et al., Carbopol dispersed PAA-modified UIO-66 with high colloidal stability as a combination nano-adjuvant boosts immune response and protection against pseudorabies virus in mice and pigs, Acta Biomater. 168 (2023) 540–550.

[25] S. Wuttke, et al., Positioning metal-organic framework nanoparticles within the context of drug delivery–a comparison with mesoporous silica nanoparticles and dendrimers, Biomaterials 123 (2017) 172–183.

[26] K. Liang, et al., Biomimetic mineralization of metal-organic frameworks as protective coatings for biomacromolecules, Nat. Commun. 6 (1) (2015) 7240.

[27] H. Li, M. Eddaoudi, M. O'Keeffe, O.M. Yaghi, Design and synthesis of an exceptionally stable and highly porous metal-organic framework, Nature 402 (6759) (1999) 276–279.

[28] X. Kong, et al., Mapping of functional groups in metal-organic frameworks, Science 341 (6148) (2013) 882–885.

[29] P. Horcajada, et al., Porous metal–organic-framework nanoscale carriers as a potential platform for drug delivery and imaging, Nat. Mater. 9 (2) (2010) 172–178.

[30] C. Tamames-Tabar, et al., Cytotoxicity of nanoscaled metal–organic frameworks, J. Mater. Chem. B 2 (3) (2014) 262–271.

[31] R. Grall, et al., In vitro biocompatibility of mesoporous metal (III; Fe, Al, Cr) trimesate MOF nanocarriers, J. Mater. Chem. B 3 (42) (2015) 8279–8292.

[32] S.K. Alsaiari, et al., Sustained and targeted delivery of checkpoint inhibitors by metal-organic frameworks for cancer immunotherapy, Sci. Adv. 7 (4) (2021) eabe7174.

[33] T. Baati, et al., In depth analysis of the in vivo toxicity of nanoparticles of porous iron (III) metal–organic frameworks, Chem. Sci. 4 (4) (2013) 1597–1607.

[34] M. Cai, et al., Amino-functionalized Zn metal organic frameworks as antitumor drug curcumin carriers, New J. Chem. 44 (41) (2020) 17693–17704.

[35] M.Z. Alyami, et al., Cell-type-specific CRISPR/Cas9 delivery by biomimetic metal organic frameworks, J. Am. Chem. Soc. 142 (4) (2020) 1715–1720.

[36] P. Horcajada, et al., Metal–organic frameworks in biomedicine, Chem. Rev. 112 (2) (2012) 1232–1268.

[37] D.v.d. Merwe, S. Tawde, J.A. Pickrell, L.E. Erickson, Nanocrystalline titanium dioxide and magnesium oxide in vitro dermal absorption in human skin, Cutan. Ocul. Toxicol. 28 (2) (2009) 78–82.

[38] P. Horcajada, et al., How linker's modification controls swelling properties of highly flexible iron (III) dicarboxylates MIL-88, J. Am. Chem. Soc. 133 (44) (2011) 17839–17847.

[39] T. Devic, et al., Functionalization in flexible porous solids: effects on the pore opening and the host– guest interactions, J. Am. Chem. Soc. 132 (3) (2010) 1127–1136.

[40] M. Eddaoudi, et al., Systematic design of pore size and functionality in isoreticular MOFs and their application in methane storage, Science 295 (5554) (2002) 469–472.

[41] T.R. Whitfield, X. Wang, L. Liu, A.J. Jacobson, Metal-organic frameworks based on iron oxide octahedral chains connected by benzenedicarboxylate dianions, Solid State Sci. 7 (9) (2005) 1096–1103.

[42] C. Serre, et al., Role of solvent-host interactions that lead to very large swelling of hybrid frameworks, Science 315 (5820) (2007) 1828–1831.

[43] S. Hou, et al., Green synthesis and evaluation of an iron-based metal–organic framework MIL-88B for efficient decontamination of arsenate from water, Dalton Trans. 47 (7) (2018) 2222–2231.

[44] M. Dan-Hardi, et al., A new photoactive crystalline highly porous titanium (IV) dicarboxylate, J. Am. Chem. Soc. 131 (31) (2009) 10857–10859.

[45] Y. Liu, ch V. Kravtsov, R. Larsen, M. Eddaoudi, Molecular building blocks approach to the assembly of zeolite-like metal-organic frameworks (ZMOFs) with extra-large cavities, Chem. Commun. 14 (2006) 1488–1490.

[46] X.C. Huang, Y.Y. Lin, J.P. Zhang, X.M. Chen, Ligand-directed strategy for zeolite-type metal–organic frameworks: zinc (II) imidazolates with unusual zeolitic topologies, Angew. Chem. Int. Ed. 45 (10) (2006) 1557–1559.

[47] R. Banerjee, et al., Control of pore size and functionality in isoreticular zeolitic imidazolate frameworks and their carbon dioxide selective capture properties, J. Am. Chem. Soc. 131 (11) (2009) 3875–3877.

[48] Z. Zhu, et al., Micro or nano: evaluation of biosafety and biopotency of magnesium metal organic framework-74 with different particle sizes, Nano Res. 13 (2020) 511–526.

[49] D. Duan, et al., Size-controlled synthesis of drug-loaded zeolitic imidazolate framework in aqueous solution and size effect on their cancer theranostics in vivo, ACS Appl. Mater. Interfaces 10 (49) (2018) 42165–42174.

[50] A. Baeza, D. Ruiz-Molina, M. Vallet-Regí, Recent advances in porous nanoparticles for drug delivery in antitumoral applications: inorganic nanoparticles and nanoscale metal-organic frameworks, Expet Opin. Drug Deliv. 14 (6) (2017) 783–796.

[51] J. Park, et al., Size-controlled synthesis of porphyrinic metal–organic framework and functionalization for targeted photodynamic therapy, J. Am. Chem. Soc. 138 (10) (2016) 3518–3525.

[52] S. Wang, et al., Modulated synthesis of monodisperse MOF-5 crystals with tunable sizes and shapes, Inorg. Chem. Commun. 93 (2018) 56–60.

[53] N. Feliu, B. Fadeel, Nanotoxicology: no small matter, Nanoscale 2 (12) (2010) 2514–2520.

[54] Y. Yao, et al., Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance, Front. Mol. Biosci. 7 (2020) 193.

[55] L. Tang, et al., Investigating the optimal size of anticancer nanomedicine, Proc. Natl. Acad. Sci. USA 111 (43) (2014) 15344–15349.

[56] J.A. Champion, Y.K. Katare, S. Mitragotri, Particle shape: a new design parameter for micro-and nanoscale drug delivery carriers, J. Contr. Release 121 (1–2) (2007) 3–9.

[57] N. ul Qadir, S.A. Said, H.M. Bahaidarah, Structural stability of metal organic frameworks in aqueous media–controlling factors and methods to improve hydrostability and hydrothermal cyclic stability, Microporous Mesoporous Mater. 201 (2015) 61–90.

[58] H. Jasuja, K.S. Walton, Effect of catenation and basicity of pillared ligands on the water stability of MOFs, Dalton Trans. 42 (43) (2013) 15421–15426.

[59] J.A. Greathouse, M.D. Allendorf, The interaction of water with MOF-5 simulated by molecular dynamics, J. Am. Chem. Soc. 128 (33) (2006) 10678–10679.

[60] L. Huang, et al., Synthesis, morphology control, and properties of porous metal–organic coordination polymers, Microporous Mesoporous Mater. 58 (2) (2003) 105–114.

[61] A. Felix Sahayaraj, et al., Metal–organic frameworks (MOFs): the next generation of materials for catalysis, gas storage, and separation, J. Inorg. Organomet. Polym. Mater. 33 (7) (2023) 1757–1781.

[62] W. Xiang, et al., Synthesis, characterization and application of defective metal–organic frameworks: current status and perspectives, J. Mater. Chem. A 8 (41) (2020) 21526–21546.

[63] J. Kim, Synthesis, Characterization, and Utilization of Metal-Organic Frameworks (MOFs) and Their Pyrolyzed Functional Carbons, University of Notre Dame, 2016.

[64] I. Chakraborty, et al., Massive electrical conductivity enhancement of multilayer graphene/polystyrene composites using a nonconductive filler, ACS Appl. Mater. Interfaces 6 (19) (2014) 16472–16475.

[65] P. Pachfule, R. Das, P. Poddar, R. Banerjee, Solvothermal synthesis, structure, and properties of metal organic framework isomers derived from a partially fluorinated link, Cryst. Growth Des. 11 (4) (2011) 1215–1222.

[66] W. Zhu, et al., Two-dimensional metal-organic-framework as a unique theranostic nano-platform for nuclear imaging and chemo-photodynamic cancer therapy, Nano Res. 12 (2019) 1307–1312.

[67] T. Kwon, et al., Optimizing hemocompatibility of surfactant-coated silver nanoparticles in human erythrocytes, J. Nanosci. Nanotechnol. 12 (8) (2012) 6168–6175.

[68] D. Liu, et al., Self-assembled nanoscale coordination polymers with trigger release properties for effective anticancer therapy, Nat. Commun. 5 (1) (2014) 4182.

[69] W. Sun, X. Zhai, L. Zhao, Synthesis of ZIF-8 and ZIF-67 nanocrystals with well-controllable size distribution through reverse microemulsions, Chem. Eng. J. 289 (2016) 59–64.

[70] J.A. Foster, et al., Liquid exfoliation of alkyl-ether functionalised layered metal–organic frameworks to nanosheets, Chem. Commun. 52 (69) (2016) 10474–10477.

[71] M. Rezaei, et al., NanoMIL-100 (Fe) containing docetaxel for breast cancer therapy, Artif. Cell Nanomed. Biotechnol. 46 (7) (2018) 1390–1401.

[72] W. Wang, L. Wang, Z. Li, Z. Xie, BODIPY-containing nanoscale metal–organic frameworks for photodynamic therapy, Chem. Commun. 52 (31) (2016) 5402–5405.

[73] C. Gupta, P. Pant, H. Rajput, Strategies to synthesize diverse metal–organic frameworks (MOFs), in: Metal-Organic Frameworks (MOFs) as Catalysts, Springer, 2022, pp. 69–97.

[74] Z. Zheng, et al., High-yield, green and scalable methods for producing MOF-303 for water harvesting from desert air, Nat. Protoc. 18 (1) (2023) 136–156.

[75] J.R. Pankhurst, et al., Metal–ligand bond strength determines the fate of organic ligands on the catalyst surface during the electrochemical CO 2 reduction reaction, Chem. Sci. 11 (34) (2020) 9296–9302.

[76] S. Mozaffari, et al., The role of nanoparticle size and ligand coverage in size focusing of colloidal metal nanoparticles, Nanoscale Adv. 1 (10) (2019) 4052–4066.

[77] J. Chang, E.R. Waclawik, Experimental and theoretical investigation of ligand effects on the synthesis of ZnO nanoparticles, J. Nanoparticle Res. 14 (2012) 1–14.

[78] W. Wang, et al., Ligand control of growth, morphology, and capping structure of colloidal CdSe nanorods, Chem. Mater. 19 (10) (2007) 2573–2580.

[79] F. Zhou, T. Peterson, Z. Fan, S. Wang, The commonly used stabilizers for phytochemical-based nanoparticles: stabilization effects, mechanisms, and applications, Nutrients 15 (18) (2023) 3881.

[80] O.M. Yaghi, H. Li, Hydrothermal synthesis of a metal-organic framework containing large rectangular channels, J. Am. Chem. Soc. 117 (41) (1995) 10401–10402.

[81] M.H. Ghasemi, V. Irani, A. Tavasoli, Amino functionalized ZIF-90@ GO/MDEA nanofluid: as a new class of multi-hybrid systems to enhance the performance of amine solutions in CO2 absorption, J. Nat. Gas Sci. Eng. 74 (2020) 103110.

[82] K.M. Taylor, W.J. Rieter, W. Lin, Manganese-based nanoscale metal– organic frameworks for magnetic resonance imaging, J. Am. Chem. Soc. 130 (44) (2008) 14358–14359.

[83] S.-Z. Lu, A. Hellawell, The mechanism of silicon modification in aluminum-silicon alloys: impurity induced twinning, Metall. Trans. A 18 (1987) 1721–1733.

[84] W.J. Rieter, K.M. Taylor, W. Lin, Surface modification and functionalization of nanoscale metal-organic frameworks for controlled release and luminescence sensing, J. Am. Chem. Soc. 129 (32) (2007) 9852–9853.

[85] T. Si, et al., Design and evaluation of novel MOF–polymer core–shell composite as mixed-mode stationary phase for high performance liquid chromatography, Microchim. Acta 188 (2021) 1–9.

[86] S. Bao, et al., A green selective water-etching approach to MOF@ mesoporous SiO2 yolk-shell nanoreactors with enhanced catalytic stabilities, Matter 3 (2) (2020) 498–508.

[87] A. Bartolazzi, R. Peach, A. Aruffo, I. Stamenkovic, Interaction between CD44 and hyaluronate is directly implicated in the regulation of tumor development, J. Exp. Med. 180 (1) (1994) 53–66.

[88] S. Kumari, et al., Biolistic delivery of liposomes protected in metal-organic frameworks, Proc. Natl. Acad. Sci. USA 120 (11) (2023) e2218247120.

[89] S. Wuttke, et al., MOF nanoparticles coated by lipid bilayers and their uptake by cancer cells, Chem. Commun. 51 (87) (2015) 15752–15755.

[90] B. Illes, et al., Exosome-coated metal–organic framework nanoparticles: an efficient drug delivery platform, Chem. Mater. 29 (19) (2017) 8042–8046.

[91] Z. Luo, et al., Light-Induced redox-responsive smart drug delivery system by using selenium-containing polymer@ MOF shell/core nanocomposite, Adv. Healthcare Mater. 8 (15) (2019) 1900406.

[92] M.J. Earle, K.R. Seddon, Ionic liquids. Green solvents for the future, Pure Appl. Chem. 72 (7) (2000) 1391–1398.

[93] R. Lin, et al., Recent advances in ionic liquids—MOF hybrid electrolytes for solid-state electrolyte of lithium battery, Batteries 9 (6) (2023) 314.

[94] L. Lupa, et al., Performance of ionic liquid functionalized metal organic frameworks in the adsorption process of phenol derivatives, RSC Adv. 14 (7) (2024) 4759–4777.

[95] M. Urgoiti-Rodriguez, et al., Exploring ionic liquid-laden metal-organic framework composite materials as hybrid electrolytes in metal (ion) batteries, Front. Chem. 10 (2022) 995063.

[96] A. Yohannes, J. Li, S. Yao, Various metal organic frameworks combined with imidazolium, quinolinum and benzothiazolium ionic liquids for removal of three antibiotics from water, J. Mol. Liq. 318 (2020) 114304.

[97] N.V. Plechkova, K.R. Seddon, Applications of ionic liquids in the chemical industry, Chem. Soc. Rev. 37 (1) (2008) 123–150.

[98] J. Liu, et al., Applications of metal–organic frameworks in heterogeneous supramolecular catalysis, Chem. Soc. Rev. 43 (16) (2014) 6011–6061.

[99] G. Lu, et al., Imparting functionality to a metal–organic framework material by controlled nanoparticle encapsulation, Nat. Chem. 4 (4) (2012) 310–316.

[100] N. Lin, et al., Biocompatible double-membrane hydrogels from cationic cellulose nanocrystals and anionic alginate as complexing drugs codelivery, ACS Appl. Mater. Interfaces 8 (11) (2016) 6880–6889.

[101] S. Awate, L.A. Babiuk, G. Mutwiri, Mechanisms of action of adjuvants, Front. Immunol. 4 (2013) 114.

[102] P. Li, et al., Toward design rules for enzyme immobilization in hierarchical mesoporous metal-organic frameworks, Chem 1 (1) (2016) 154–169.

[103] T. Betancourt, A. Doiron, K.A. Homan, L. Brannon-Peppas, Controlled release and nanotechnology, Nanotechnology in drug delivery (2009) 283–312.

[104] Y. Wang, Z. Li, J. Ouyang, G.E. Karniadakis, Controlled release of entrapped nanoparticles from thermoresponsive hydrogels with tunable network characteristics, Soft Matter 16 (20) (2020) 4756–4766.

[105] R.A. Siegel, M.J. Rathbone, Overview of controlled release mechanisms, in: Fundamentals and Applications of Controlled Release Drug Delivery, Springer, 2011, pp. 19–43.

[106] B. Tousian, A.R. Khosravi, Chitosan-based pulmonary particulate systems for anticancer and antiviral drug carriers: a promising delivery for COVID-19 vaccines, Results in Chemistry 6 (2023) 101146.

[107] B. Tousian, M.H. Ghasemi, A.R. Khosravi, Targeted chitosan nanoparticles embedded into graphene oxide functionalized with caffeic acid as a potential drug delivery system: new insight into cancer therapy, Int. J. Biol. Macromol. 222 (2022) 295–304.

[108] K. Elumalai, S. Srinivasan, A. Shanmugam, Review of the efficacy of nanoparticle-based drug delivery systems for cancer treatment, Biomedical Technology 5 (2024) 109–122.

[109] N. Thakur, et al., Nanoparticles as smart carriers for enhanced cancer immunotherapy, Front. Chem. 8 (2020) 597806.

[110] J. Zhang, et al., Nanoparticle-based drug delivery systems to enhance cancer immunotherapy in solid tumors, Front. Immunol. 14 (2023) 1230893.

[111] F. Carraro, et al., MOFs and biomacromolecules for biomedical applications, in: P. Horcajada Cortés, S. Rojas Macías (Eds.), Metal-Organic Frameworks in Biomedical and Environmental Field, Springer International Publishing, Cham, 2021, pp. 379–432.

[112] W. Duan, et al., State-of-the-Art and prospects of biomolecules: incorporation in functional metal–organic frameworks, Top. Curr. Chem. 377 (6) (2019) 34.

[113] Y. Lin, Y. Huang, X. Chen, Recent advances in metal-organic frameworks for biomacromolecule sensing, Chemosensors 10 (10) (2022) 412.

[114] P.-H. Tong, et al., Metal–organic frameworks (MOFs) as host materials for the enhanced delivery of biomacromolecular therapeutics, Chem. Commun. 57 (91) (2021) 12098–12110.

[115] Y. Sun, et al., Metal–organic framework nanocarriers for drug delivery in biomedical applications, Nano-Micro Lett. 12 (1) (2020) 103.

[116] E.S. Pena, et al., Metal–organic coordination polymers for delivery of immunomodulatory agents, and infectious disease and cancer vaccines, Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology (2023) e1877.

[117] A. Ringaci, et al., Metal-organic frameworks for simultaneous gene and small molecule delivery in vitro and in vivo, Chem. Eng. J. 418 (2021) 129386.

[118] X. Li, X. Wang, A. Ito, N.M. Tsuji, A nanoscale metal organic frameworks-based vaccine synergises with PD-1 blockade to potentiate anti-tumour immunity, Nat. Commun. 11 (1) (2020) 3858.

[119] Y. Ma, et al., Metal-organic frameworks and their composites towards biomedical applications, Front. Mol. Biosci. 8 (2021) 805228.

[120] S. Zimmermann, A. Dalpke, K. Heeg, CpG oligonucleotides as adjuvant in therapeutic vaccines against parasitic infections, International Journal of Medical Microbiology 298 (1–2) (2008) 39–44.

[121] K. Zhang, et al., Preparation and performance study of COS/PEI@ PolyI: C/OVA nanocomposite using the blend system of chitooligosaccharide and polyethyleneimine as a drug carrier, Macromol. Res. 29 (2021) 800–809.

[122] Y. Mishra, et al., Aptamers versus vascular endothelial growth factor (VEGF): a new battle against ovarian cancer, Pharmaceuticals 16 (6) (2023) 849.

[123] Q. Lei, et al., Ultrasound-responsive metal–organic framework-based nanosystem for sonodynamic therapy/amplified ferroptosis/Ido-blockade osteosarcoma immunotherapy, Chem. Eng. J. 490 (2024) 151614.

[124] Y. Liu, et al., Nanoengineering of vaccine nanoparticles via templating of metal–organic frameworks for tumor immunotherapy, Chem. Mater. 36 (10) (2024) 5017–5027.

[125] X. Li, et al., A facile approach to preparing personalized cancer vaccines using iron-based metal organic framework, Front. Immunol. 14 (2024) 1328379.

[126] Y. Zhang, et al., Metal-organic-framework-based vaccine platforms for enhanced systemic immune and memory response, Adv. Funct. Mater. 26 (35) (2016) 6454–6461.

[127] Z. Li, et al., Functional groups influence and mechanism research of UiO-66-type metal-organic frameworks for ketoprofen delivery, Colloids Surf. B Biointerfaces 178 (2019) 1–7.

[128] C.Y. Sun, et al., Chiral nanoporous metal-organic frameworks with high porosity as materials for drug delivery, Adv. Mater. 23 (47) (2011) 5629–5632.

[129] S. Rojas, et al., Nanoscaled zinc pyrazolate metal–organic frameworks as drug-delivery systems, Inorg. Chem. 55 (5) (2016) 2650–2663.

[130] X. Hu, et al., Nanoporous CD-MOF particles with uniform and inhalable size for pulmonary delivery of budesonide, Int. J. Pharm. 564 (2019) 153–161.

[131] M. Marcos-Almaraz, et al., Towards improved HIV-microbicide activity through the co-encapsulation of NRTI drugs in biocompatible metal organic framework nanocarriers, J. Mater. Chem. B 5 (43) (2017) 8563–8569.

[132] K. Sun, et al., Functionalization of mixed ligand metal-organic frameworks as the transport vehicles for drugs, J. Colloid Interface Sci. 486 (2017) 128–135.

[133] C. He, K. Lu, D. Liu, W. Lin, Nanoscale metal–organic frameworks for the co-delivery of cisplatin and pooled siRNAs to enhance therapeutic efficacy in drug-resistant ovarian cancer cells, J. Am. Chem. Soc. 136 (14) (2014) 5181–5184.

[134] L. Wang, et al., Specific determination of HBV using a viral aptamer molecular imprinting polymer sensor based on ratiometric metal organic framework, Microchim. Acta 188 (7) (2021) 221.

[135] P.M. Chen, et al., Bioinspired engineering of a bacterium-like metal–organic framework for cancer immunotherapy, Adv. Funct. Mater. 30 (42) (2020) 2003764.

[136] Z. Wei, et al., Engineered Iron-Based nanoplatform amplifies repolarization of M2-Like Tumor-Associated Macrophages for enhanced cancer immunotherapy, Chem. Eng. J. 433 (2022) 133847.

[137] J. Zhou, et al., Biomimetic nanotechnology toward personalized vaccines, Adv. Mater. 32 (13) (2020) 1901255.

[138] C. Zhang, K. Pu, Molecular and nanoengineering approaches towards activatable cancer immunotherapy, Chem. Soc. Rev. 49 (13) (2020) 4234–4253.

[139] K.T. Gause, et al., Immunological principles guiding the rational design of particles for vaccine delivery, ACS Nano 11 (1) (2017) 54–68.

[140] R.L. Coffman, A. Sher, R.A. Seder, Vaccine adjuvants: putting innate immunity to work, Immunity 33 (4) (2010) 492–503.

[141] A. Facciolà, G. Visalli, A. Laganà, A. Di Pietro, An overview of vaccine adjuvants: current evidence and future perspectives, Vaccines 10 (5) (2022) 819.

[142] B. Pulendran, R. Ahmed, Immunological mechanisms of vaccination, Nat. Immunol. 12 (6) (2011) 509–517.

[143] Y. Cui, M. Ho, Y. Hu, Y. Shi, Vaccine adjuvants: current status, research and development, licensing, and future opportunities, J. Mater. Chem. B 12 (17) (2024) 4118–4137.

[144] C. Li, et al., Cyclodextrin metal-organic framework as vaccine adjuvants enhances immune responses, Drug Deliv. 28 (1) (2021) 2594–2602.

[145] B.S. Ou, O.M. Saouaf, J. Baillet, E.A. Appel, Sustained delivery approaches to improving adaptive immune responses, Adv. Drug Deliv. Rev. 187 (2022) 114401.

[146] K. Sun, et al., Reinforcing the induction of immunogenic cell death via artificial engineered cascade bioreactor-enhanced chemo-immunotherapy for optimizing cancer immunotherapy, Small 17 (37) (2021) 2101897.

[147] G. Chong, et al., Bioengineering of nano metal-organic frameworks for cancer immunotherapy, Nano Res. 14 (5) (2021) 1244–1259.

[148] D.N. Desai, et al., Nanoadjuvants: promising bioinspired and biomimetic approaches in vaccine innovation, ACS Omega 8 (31) (2023) 27953–27968.

[149] J. Lu, et al., Ultrafast rectifying counter-directional transport of proton and metal ions in metal-organic framework–based nanochannels, Sci. Adv. 8 (14) (2022) eabl5070.

[150] Z.S. Stillman, et al., Aluminum-based metal–organic framework nanoparticles as pulmonary vaccine adjuvants, J. Nanobiotechnol. 21 (1) (2023) 39.

[151] N. Tyagi, Y.H. Wijesundara, J.J. Gassensmith, A. Popat, Clinical translation of metal–organic frameworks, Nat. Rev. Mater. 8 (11) (2023) 701–703.

[152] M.I.o. Technology, New Type of Nanoparticle Makes Vaccines More Powerful, 2024. https://www.sciencedaily.com/releases/2024/03/240306150424.htm.

[153] S.K. Alsaiari, et al., Zeolitic imidazolate frameworks activate endosomal Toll-like receptors and potentiate immunogenicity of SARS-CoV-2 spike protein trimer, Sci. Adv. 10 (10) (2024) eadj6380.

[154] C. Huang, et al., Boosting humoral and cellular immunity with enhanced STING activation by hierarchical mesoporous metal-organic framework adjuvants, J. Contr. Release 370 (2024) 691–706.

[155] R.N. Ehrman, et al., A scalable synthesis of adjuvanting antigen depots based on metal–organic frameworks, Chem. Sci. 15 (8) (2024) 2731–2744.

[156] L. Wu, et al., Enzyme-responsive multifunctional peptide coating of gold nanorods improves tumor targeting and photothermal therapy efficacy, Acta Biomater. 86 (2019) 363–372.

[157] H. He, et al., Redox responsive metal organic framework nanoparticles induces ferroptosis for cancer therapy, Small 16 (33) (2020) 2001251.

[158] J. Zhao, et al., Dual-responsive metal organic framework for electrically-enhanced cascade catalytic tumor therapy, Materials Today Advances 17 (2023) 100329.

[159] W. Cai, C.C. Chu, G. Liu, Y.X.J. Wáng, Metal–organic framework-based nanomedicine platforms for drug delivery and molecular imaging, Small 11 (37) (2015) 4806–4822.

[160] G. Chong, et al., Bioengineering of nano metal-organic frameworks for cancer immunotherapy, Nano Res. 14 (2021) 1244–1259.

[161] B. Liu, et al., Metal-organic frameworks functionalized with nucleic acids and amino acids for structure-and function-specific applications: a tutorial review, Chem. Eng. J. 428 (2022) 131118.

[162] V.A. Tran, V. Thuan Le, V.D. Doan, G.N. Vo, Utilization of functionalized metal–organic framework nanoparticle as targeted drug delivery system for cancer therapy, Pharmaceutics 15 (3) (2023) 931.

[163] S. Wu, et al., Peptide-functionalized metal-organic framework nanocomposite for ultrasensitive detection of secreted protein acidic and rich in cysteine with practical application, Biosens. Bioelectron. 169 (2020) 112613.

[164] F. Lyu, et al., One-pot synthesis of protein-embedded metal–organic frameworks with enhanced biological activities, Nano Lett. 14 (10) (2014) 5761–5765.

[165] X. Lian, et al., Enzyme–MOF (metal–organic framework) composites, Chem. Soc. Rev. 46 (11) (2017) 3386–3401.

[166] R. Xiong, et al., Evaluation of functionalized isoreticular metal organic frameworks (IRMOFs) as smart nanoporous preconcentrators of RDX, Sensor. Actuator. B Chem. 148 (2) (2010) 459–468.

[167] D. Feng, et al., Robust and conductive two-dimensional metal– organic frameworks with exceptionally high volumetric and areal capacitance, Nat. Energy 3 (1) (2018) 30–36.

[168] H. Zheng, et al., One-pot synthesis of metal–organic frameworks with encapsulated target molecules and their applications for controlled drug delivery, J. Am. Chem. Soc. 138 (3) (2016) 962–968.

[169] Z. Hu, B.J. Deibert, J. Li, Luminescent metal–organic frameworks for chemical sensing and explosive detection, Chem. Soc. Rev. 43 (16) (2014) 5815–5840.

[170] S.R. Miller, et al., A rare example of a porous Ca-MOF for the controlled release of biologically active NO, Chem. Commun. 49 (71) (2013) 7773–7775.

[171] C. Wang, D. Liu, W. Lin, Metal–organic frameworks as a tunable platform for designing functional molecular materials, J. Am. Chem. Soc. 135 (36) (2013) 13222–13234.

[172] X.-f. Zhong, X. Sun, Nanomedicines based on nanoscale metal-organic frameworks for cancer immunotherapy, Acta Pharmacol. Sin. 41 (7) (2020) 928–935.

[173] Y. Guo, et al., Construction of nanocarriers based on endogenous cell membrane and their application in nanomedicine, Chin. J. Chem. 40 (13) (2022) 1623–1640.

[174] R.H. Fang, W. Gao, L. Zhang, Targeting drugs to tumours using cell membrane-coated nanoparticles, Nat. Rev. Clin. Oncol. 20 (1) (2023) 33–48.

[175] W.L. Liu, et al., Recent advances of cell membrane-coated nanomaterials for biomedical applications, Adv. Funct. Mater. 30 (39) (2020) 2003559.

[176] J. Yang, et al., Smart biomimetic metal organic frameworks based on ROS-ferroptosis-glycolysis regulation for enhanced tumor chemo-immunotherapy, J. Contr. Release 334 (2021) 21–33.

[177] J. Luo, et al., Enhancement of antitumor immunotherapy using mitochondria-targeted cancer cell membrane-biomimetic MOF-mediated sonodynamic therapy and checkpoint blockade immunotherapy, J. Nanobiotechnol. 20 (1) (2022) 1–17.

[178] H. Wang, C. Wu, X. Tong, S. Chen, A biomimetic metal-organic framework nanosystem modulates immunosuppressive tumor microenvironment metabolism to amplify immunotherapy, J. Contr. Release 353 (2023) 727–737.

[179] M. Xu, et al., Transforming cold tumors into hot ones with a metal–organic framework-based biomimetic nanosystem for enhanced immunotherapy, ACS Appl. Mater. Interfaces 15 (14) (2023) 17470–17484.

[180] H. Ding, et al., Advances and prospects of tumor immunotherapy mediated by immune cell-derived biomimetic metal-organic frameworks, Colloids Surf. B Biointerfaces (2023) 113607.

[181] Y. Song, et al., A bimetallic metal–organic-framework-based biomimetic nanoplatform enhances anti-leukemia immunity via synchronizing DNA demethylation and RNA hypermethylation, Adv. Mater. 35 (16) (2023) 2210895.

[182] B. Li, M. Ashrafizadeh, T. Jiao, Biomedical application of metal-organic frameworks (MOFs) in cancer therapy: stimuli-responsive and biomimetic nanocomposites in targeted delivery, phototherapy and diagnosis, Int. J. Biol. Macromol. (2024) 129391.

[183] T. Tao, et al., Biomimetic camouflaged metal organic framework for enhanced siRNA delivery in tumor environment, J. Mater. Chem. B 2024 (12) (2024) 4080–4096.

[184] S. Sun, et al., Enhancing cell pyroptosis with biomimetic nanoparticles for melanoma chemo-immunotherapy, J. Contr. Release 367 (2024) 470–485.

[185] F. Liu, et al., Manganese-based microcrystals equipped with Ythdf1-targeted biomimetic nanovaccines for reinforced dendritic cell spatiotemporal orchestration, Nano Today 54 (2024) 102112.

[186] Z. Chen, et al., Biomimetic MOF-based nano-immunoactivator via disruption of ion homeostasis for strengthened tumor microwave-immunotherapy, Adv. Funct. Mater. (2024) 2401359.

[187] T. Hidalgo, R. Simón-Vázquez, A. González-Fernández, P. Horcajada, Cracking the immune fingerprint of metal–organic frameworks, Chem. Sci. 13 (4) (2022) 934–944.

[188] M.d.J. Velásquez-Hernández, et al., Towards applications of bioentities@ MOFs in biomedicine, Coord. Chem. Rev. 429 (2021) 213651.

[189] S. Wang, et al., H3K27me3 depletion during differentiation promotes myogenic transcription in porcine satellite cells, Genes 10 (3) (2019) 231.

[190] G. Gocheva, A. Ivanova, A look at receptor–ligand pairs for active-targeting drug delivery from crystallographic and molecular dynamics perspectives, Mol. Pharm. 16 (8) (2019) 3293–3321.

[191] E.M. Benchafia, et al., Cubic gauche polymeric nitrogen under ambient conditions, Nat. Commun. 8 (1) (2017) 930.

[192] E.S. Pena, et al., Metal–organic coordination polymers for delivery of immunomodulatory agents, and infectious disease and cancer vaccines, Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology 15 (4) (2023) e1877.

[193] J. Takaya, Catalysis using transition metal complexes featuring main group metal and metalloid compounds as supporting ligands, Chem. Sci. 12 (6) (2021) 1964–1981.

[194] V.K. Srivastava, Synthesis, characterization, and biological studies of some biometal complexes, Future Journal of Pharmaceutical Sciences 7 (2021) 1–11.