

## Review

# Metal-Organic Framework Nanoparticle-Based Biomineralization: A New Strategy toward Cancer Treatment

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Received: 2019.01.27; Accepted: 2019.03.20; Published: 2019.05.18

## Abstract

Cancer treatment using functional proteins, DNA/RNA, or complex bio-entities is important in both preclinical and clinical studies. With the help of nano-delivery systems, these biomacromolecules can enrich cancer tissues to match the clinical requirements. Biomineralization *via* a self-assembly process has been widely applied to provide biomacromolecules exoskeletal-like protection for immune shielding and preservation of bioactivity. Advanced metal-organic framework nanoparticles (MOFs) are excellent supporting matrices due to the low toxicity of polycarboxylic acids and metals, high encapsulation efficiency, and moderate synthetic conditions. In this review, we study MOFs-based biomineralization for cancer treatment and summarize the unique properties of MOF hybrids. We also evaluate the outlook of potential cancer treatment applications for MOFs-based biomineralization. This strategy likely opens new research orientations for cancer theranostics.

Key words: metal-organic framework; biomineralization; cancer treatment; theranostics

## 1. Introduction

Cancer is an urgent global public problem and the focus of significant worldwide research [1-3]. Cancer treatments include low-molecular-weight drugs, gene therapy *via* DNA/RNA [4], immunotherapy *via* antibodies and antigens [5], and biotherapy *via* proteins and oncolytic viruses [6]. However, these biological approaches are limited by the complicated tumor microenvironment, so the delivery systems were studied for the application of the biomacromolecules. These traditional delivery system were designed to load the biomacromolecules on the surface of the nanomaterials, or coated inner

the nanomaterials while the self-assembly of the polymer or amphipathic molecule. And, with help of the target modification, the biomacromolecules could gather in the function tissues/cells.

Recently, many researchers have focused on metal-organic frameworks (MOFs), which are novel porous materials [7-11]. MOFs are constructed by the coordination of metal cations or clusters and organic bridging ligands. They offer a tunable design and a network structure with controlled chemical functionality, high crystallinity, and good porosity. Due to their unique structures and properties, MOFs

have been applied in gas storage and separations [12], catalysis [13, 14], energy [15, 16], and sensing [17, 18].

Nanomedicines were designed to overcome biological barriers and selectively target tissues. They are efficient therapeutics [19]. MOFs can be tailored for specific biomedical applications [20-23]. MOFs are promising platforms for molecular imaging or drug delivery because of their porosity, tunable design, and low toxicity [24-28]. Furthermore, MOFs were also good delivery platforms for the biomacromolecules and the loading strategies of biomacromolecules can be categorized in four ways: (i) the biomacromolecule was adsorbed on the surface of MOFs due to the physical absorption [29-30]; (ii) the biomacromolecule was conjugated on the surface through the chemical coupling with the organic bridging ligands or the chelation reactions with the chelation reactions [31-33]; (iii) the biomacromolecule was infiltrated into the pore taking advantage of the mesoporous nanostructure [34-37]; (iv) the biomacromolecule was encapsulated within the MOFs networks during the self-assembly reaction of the mixed solution containing metal cations, organic bridging ligands and the biomacromolecules [38-40].

These MOF biocomposites obtained by surface coating or bio-conjugation enabled the biomacromolecule in the outermost surface, which the MOFs mostly serve as the carrier but leads to insufficient protection of biomacromolecules. While the biomacromolecules loaded on the pore networks of MOFs could protect the biomacromolecules from the external environment, and yet the infiltration strategy was dependent on pore size of the MOFs, in which the pore size must exceed the biomacromolecule.

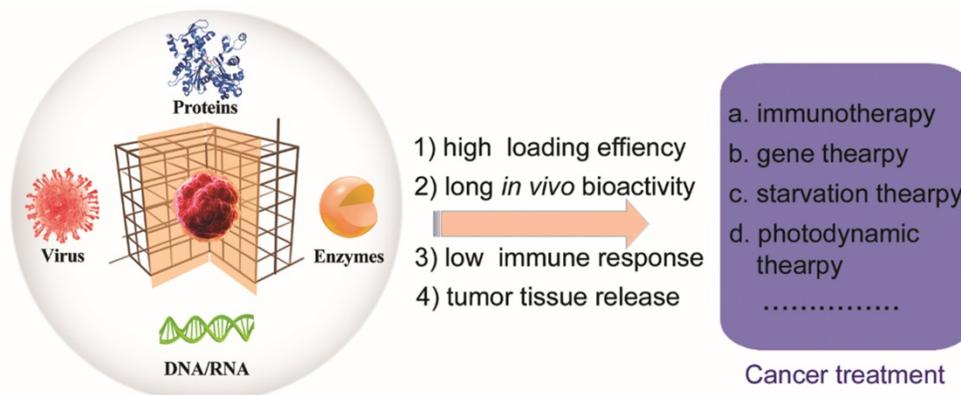
During the self-assembly (biomineralization), the activity of the biomolecules or living organisms are retained and even improved in some cases [41-44]. The diversity of the metal-connecting points and organic-bridging ligands as well as straightforward self-assembly makes MOFs excellent supporting

matrices for the immobilization of DNA, enzymes, peptides, proteins and living organisms (e.g., viruses and cells) (Figure 1) [22]. Furthermore, these surface-coated matrices of MOFs help the biomolecules or living organisms with prolonged bio-activity to enhance their stability under physiological conditions. MOFs-based biomineralization has been applied for storage, transport, treatment, and sensing. Cargo includes biological catalysts, biomolecules, or living organisms [41].

In this review, we summarize the application of MOFs-based biomineralization in cancer treatment (Figure 1). We discuss potential obstacles for practical use including toxicity arising from unintended interactions of MOFs with healthy organisms and the relevant implications for rational design. We also detail relevant insights into future applications of MOFs and how nano-bio interactions will be key to the safe design of MOFs as a platform for cancer treatment.

## 2. MOFs-based biomineralization of proteins

Protein-based pharmaceuticals (Pps), a kind of high-molecular weight therapeutic substance (>1kDa), have emerged as dominant tools (including cytokines, therapeutic antibody, protease and protein vaccines) in the treatment of various cancer [45]. Compared with traditional small molecule chemotherapeutics, Pps have tunable properties, increased therapeutic efficacy and reduced systemic toxicity [46-50]. Since rituximab was approval for lymphoma target therapy in 1997, therapeutic proteins have become a fast-growing category among cancer therapeutic drugs [51-62]. Data from various La Merie financial reports indicate that total sales of Pps in 2017 reached \$188 billion, and the rapid growth will continue over the next several years.



**Figure 1.** MOFs-based biomineralization of proteins, enzymes, DNA/RNA and virus, and their applications in cancer treatment.

**Table 1.** Summary of preparations and applications of the protein-biomaterialized MOFs.

MOF	Protein	Size	Application	Ligand	Metal ion	Temperature	Time	Ref.
ZIF-8	BSA, HSA, OVA, HRP, insulin, hemoglobin, lysozyme	1-5 $\mu\text{m}$	Bioprocessing or delivery	2-methylimidazole (BSA)	Zn <sup>2+</sup> (BSA)	Rt (BSA)	12 h (BSA)	[22]
ZIF-90	catalase	~1.5 $\mu\text{m}$	Biocatalysis	Dithiodiglycolic acid ( disulfide )	Mn <sup>2+</sup>	150 °C	24 h	[74]
ZIF-8	GOx	>1 $\mu\text{m}$	Biocatalysis	2-methylimidazole	Zn <sup>2+</sup>	4 °C	12 h	[127]
NU-1003	organophosphorus acid anhydrolase (OPAA)	300 nm (minimum size)	Biocatalysis	benzoic acid	Zr <sup>4+</sup>	80 °C	1 h	[145]
ZIF-8	urease	120-500 nm	Bioprocessing	2-methylimidazole	Zn <sup>2+</sup>	Rt	Over-night	[146]
NPCN-333	tyrosinase	100 nm	Biocatalysis and cancer therapy	4,4',4''-s-triazine-2,4,6-triyl-tribenzoic acid (TATB)	Al <sup>3+</sup>	95 °C	24 h	[147]
ZIF-8	insulin/GOx, GOx/HRP or $\beta$ -Gal/GOx/HRP	~ 500 nm	Biocatalysis	2-methylimidazole (insulin)	Zn <sup>2+</sup> (insulin)	/	Over-night	[137, 143]
ZIF-8	BSA (DOX)	70-110 nm	Cancer drug delivery	2-methylimidazole	Zn <sup>2+</sup>	/	10 min	[148]
ZIF-8	OVA	~ 200 nm	immunotherapy	2-methylimidazole	Zn <sup>2+</sup>	Rt	10 min	[109]
ZIF-8	BSA	53-153 nm	Bioprocessing for cancer treatment	2-methylimidazole	Zn <sup>2+</sup>	30 °C	20 min	[75]
ZIF-8	BSA, cytochrome c or gelonin	< 100 nm	Bioprocessing for cancer treatment	2-methylimidazole (BSA)	Zn <sup>2+</sup> (BSA)	/	50 min (BSA)	[88]

The predominance of protein-based biopharmaceuticals is likely to remain among the anticancer drugs in the foreseeable future. For example, monoclonal antibody is one of the most successful anticancer biopharmaceuticals, which has been developed and applied to treat various cancers (e.g., breast cancer, colorectal cancer, lung cancer, et al.). As the fastest growing segment of the biopharmaceutical market, protein-based biopharmaceuticals have significantly extended the lives of many cancer patients. However, proteins are xenobiotics that can elicit adverse immune reactions [6], and may lose their biological activity or even be degraded at low pH and near proteolytic enzymes in the tumor microenvironment [63-65]. With the help of advanced delivery nanosystems, bioactive proteins can be efficiently delivered to the tumor tissues/cells for targeted anticancer theranostics.

The encapsulation of protein in MOF architectures provides a novel strategy for its efficient loading without concerning the size of the biomolecules [41, 66-67]. The co-precipitation during the self-assembly procedure of the MOFs precursor solution containing the protein is a one-pot embedding. Furthermore, the addition of the protein also promotes the rapid growth of MOFs. To date, the study of the MOFs biomaterialized proteins has attracted the researchers a wide range of interests, and the applicability of this strategy has demonstrated toward different proteins and MOFs (Table 1).

Recently, Liang *et al.* reported a simple approach to encapsulate bovine serum albumin (BSA) and horseradish peroxidase (HRP) into MOFs by *de novo* assembly [11]. This is especially useful for biomaterialization through the crystal growth of the zeolitic imidazolate framework-8 (ZIF-8) using Zn(II) ion and 2-methylimidazole (2-MIM). The controlled crystal formation enabled each BSA to be encapsulated with ~22 Zn(II) ion and ~31 2-MIM; the

protein encapsulation efficiencies were 82% to even near 100% for different proteins. More importantly, the encapsulated proteins retained bioactivity at elevated temperatures, low pH, and organic solvents, leading to improved outcomes.

In another example, Feng *et al.* reported the preparation of Antibody@MOFs by a facile biomaterialization procedure [68]. The *in vitro* self-assembly reaction could protect the antibodies in the framework, and the antibodies could release within 10 s. After encapsulated by the ZIF-90 or ZIF-8, the Human immunoglobulin G (IgG) polyclonal antibody (H-IgG) and Goat anti BSA IgG polyclonal antibody (G-IgG) could show few aggregations in the harsh condition including high temperature (75 °C), methanol or acetone, freeze-thawing cycles (-80 °C~37 °C) and high pressure (20 Mpa). Furthermore, the adalimumab (Ada) was biomaterialized by ZIF-90 or ZIF-8 with high encapsulation efficiencies, and high recover efficiencies. After treated with 5 °C heat or 5 days storage plus 10 freeze-thawing cycles, the protected Ada could recover high bioactivities.

The good protection effect was quite an advantage for the protein@MOFs to adapt the complex tumor environment, and showed potential application to the cancer treatment. The protein@MOFs must possess good biocompatibility and low immunological risks [69-73]. In addition, most of the early MOFs-based biomaterialization of protein used micron-sized carriers display limitations *in vivo* applications (Table 1) [22, 74]. With the development of the MOF preparation, the size, Zeta potential, and biocompatibility of some protein-encapsulated MOFs could match the needs of nanomedicine. In 2018, Chen *et al.* synthesized BSA@ZIF-8 NPs with a size of 92 ± 7.9 nm. The encapsulation efficiency was 93%, and the BSA loading capacity was ~52.2  $\mu\text{g}$  in 1 mg BSA@ZIF-8 NPs—these were useful for intracellular studies [75].

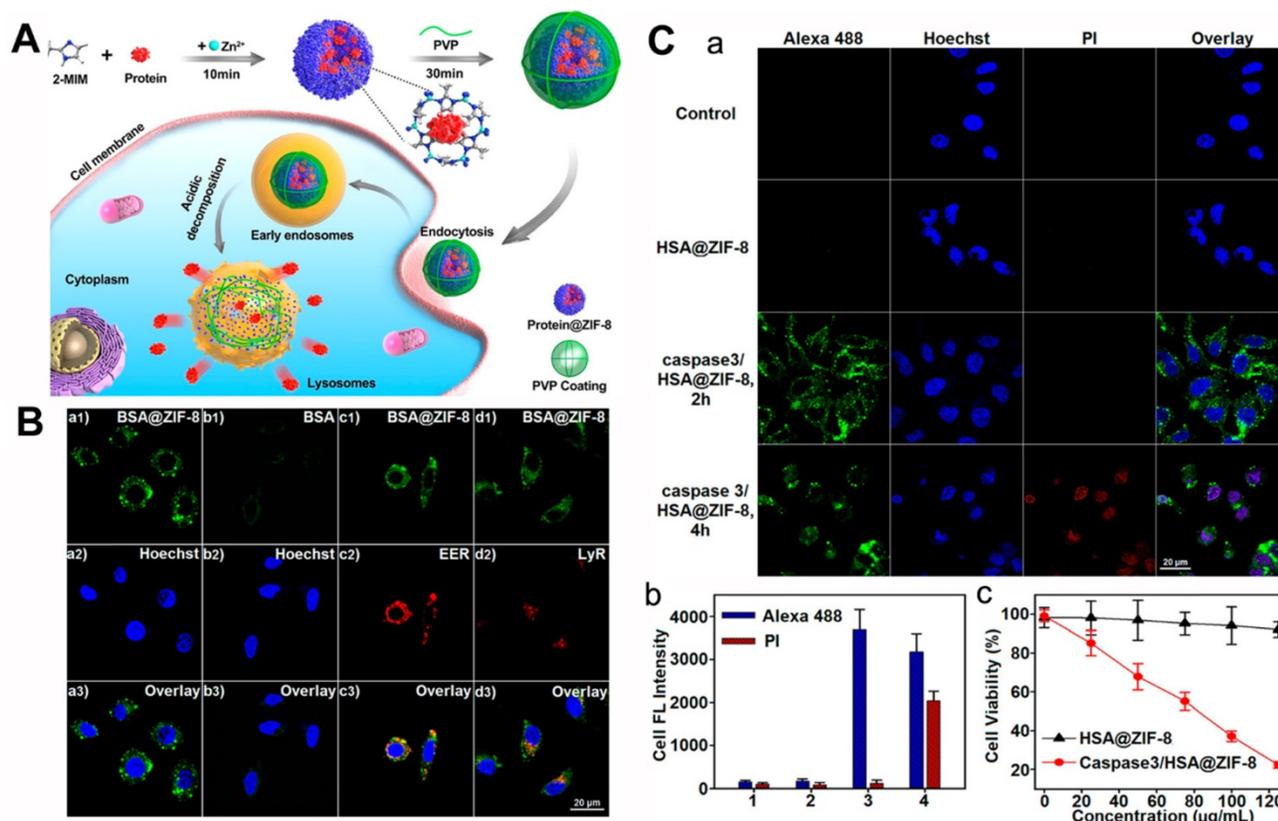
The BSA delivery system was also extended to other proteins and even multiple proteins in one single ZIF-8 NPs for co-delivery with high loading capacities; only the size changed. This might be due to the different pre-nucleated clusters surrounding the proteins.

The protein-encapsulated ZIF-8 NPs was further coated with a layer of polyvinylpyrrolidone (PVP) to enhance its stability in cell media (Figure 2). The BSA@MOF hybrid could decompose in acidic buffer (pH = 5.5), and the BSA was released within 0.5 h and completed after 2 h. Next, the fluorescein (FITC)-labeled BSA was incubated in the ZIF-8 NPs, and the resulting MOF hybrid offered much higher FITC fluorescence than the pure BSA in the HeLa cells, implying that the PVP-coated MOF hybrid improved the delivery efficiency of protein. In addition, the cell fluorescence study of the early endosomes and lysosomes indicated that the endocytic pathway accounted for the MOF hybrid. Notably, the ZIF-8 NPs could be decomposed in the weakly acid environment of early endosomes and lysosomes. The encapsulated protein was then released into the cytoplasm. The development of the

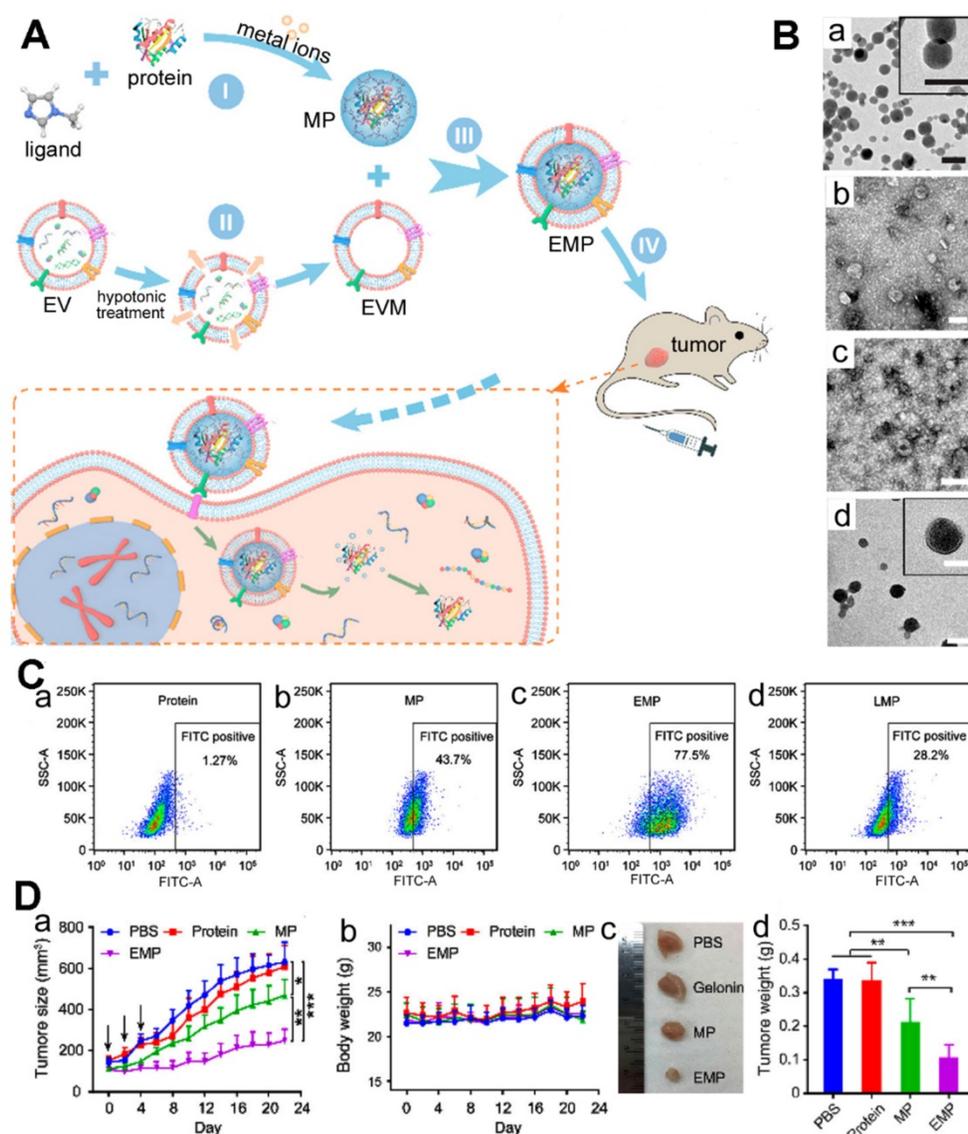
MOF hybrid could enable the proteins delivered to the live cell and escaped from the endo-lysosomes to avoid degradation/denaturation. Thus, the biomineralized MOF designed with this rationale holds great potential for cancer theranostics.

### (I) Therapeutic proteins

Nowadays, many therapeutic proteins were applied in the cancer therapy. However, the systemic delivery of therapeutic proteins to target cancer sites is impeded by many factors including rapid degradation and systemic elimination of 'naked' proteins in biological systems. A variety of delivery nanosystems have been invented to deliver therapeutic proteins to target cancer tissues [76-79]. For example, the tumor necrosis factor-related apoptosis inducing ligand (TRAIL) could induce the apoptosis of cancer cells sparing normal tissue [80-83]. To effective delivery the TRAIL ligands, Lin *et al* applied a micellar hybrid nanoparticle to carry TRAIL (IPN@TRAIL) [6]. The IPN@TRAIL could localize to the tumor tissues, and the TRAIL therapeutic efficiency enhanced by TRAIL nano-vectorization.



**Figure 2.** (A) Illustration of MOFs-based biomineralization and surface modification, and the intracellular delivery of MOF hybrid. (B) The cell fluorescence of BSA@MOF hybrid (a), FITC-BSA (b), BSA@MOF hybrid and early endosomes localized EER (c), BSA@MOF hybrid and lysosome localized LyR (d). (C) The study of the caspase 3/HSA@ MOF hybrid: (a) The cell fluorescence of HSA and caspase 3 co-encapsulated MOF hybrid. (b) The fluorescence intensity of control cells (1), HSA@MOF hybrid (2), caspase 3/HSA@ MOF hybrid 2 h (3) and 4 (4). (c) The cell viability after treatment with different MOF hybrids [75]. Copyright 2018 American Chemical Society.



**Figure 3.** (A) Schematic illustration of the EMP nanoparticles and the application of the intracellular delivery system. (B) TEM images of MP (a), EVs (b), EVM (c), and EMP (d) nanoparticles, scale bars: 100 nm. (C) The flow cytometry analysis study of the bare protein (a), MP (b), EMP (c) and LMP (d) nanoparticles incubated MDA-MB-231 cells. (D) The tumor growth curves (a), body weight variation (b) after injected intravenously with PBS, gelonin, MP and EMP nanoparticles (n = 5). \*P < 0.05, \*\*P < 0.01. The MDA-MB-231 xenograft tumors images (c) and the weights (d) after different treatments [88]. Copyright 2018 American Chemical Society.

The MOFs-based biomineralization delivery system was also investigated for cancer-associated theranostic proteins. Caspase 3 could induce the death of cells [84-86], and prior work co-encapsulated caspase 3/HSA in ZIF-8 NPs with a further PVP coating [75, 87]. When the HeLa cells were treated with caspase 3/HSA@MOF hybrid, the caspase 3 could be delivered to the cancer cells, and the cell plasma membrane was damaged. Further cell viability studies suggested that the caspase 3/HSA@MOF hybrid had obvious cytotoxicity that varied with concentration; no cytotoxicity was found for the HSA@MOF hybrid.

In another example, Cheng *et al.* also encapsulated protein using the biomineralization of ZIF-8 (Figure 3) [88]. With the modified procedure,

the encapsulation efficiency of the MOF-protein (MP) was 94%, and the protein loading capacity was as high as 41%. This was 3 to 50 times that of surface conjugation or adsorption loading. The biomineralized MOFs retained their nanostructure in PBS (pH = 7.4) but degraded in acidic buffer (pH = 5.0) after 1 h with the cargo releasing. Previous studies have demonstrated that extracellular vesicle (EV) could enhance blood circulation time, reduce phagocyte uptake, and preferentially gather in the homotypic tumor area [89-93]. These authors coated EVs on the surface of MP nanoparticles to increase the physiological solution stability and then used them for cancer therapy. In MDA-MB-231 cells, the pure gelonin showed low protein transduction efficiency (~1.27%), but the MP nanoparticles obviously

promoted the transduction efficiency (~43.7%). Furthermore, after coated with EV, the prepared EV-MOF-protein (EMP) enabled the transduction efficiency increased to ~77.5%, far higher than the liposome-enveloped MP nanoparticles. An *in vivo* study with MDA-MB-231 tumor-bearing mice demonstrated that the multifunctional MOFs could accumulate in the tumor area after intravenous injected 24 h. The mice treated with EMP nanoparticles could effectively inhibit the tumor growth than the other groups and the collected tumors were less than the other groups, implying the good protein delivery effect of the prepared biomaterialization system.

Protein-MOFs possess the following advantages: i) The biomaterialized MOFs have an extremely high protein loading capacity relative to the surface modification; ii) The MOFs protect therapeutic protein from enzyme degradation in the circulation and tumor microenvironment, and maintained the bioactivity in the cancer cells; iii) The MOFs can degrade in the weakly acidic solution, leading to the encapsulated proteins being released from the MOFs structure in the acidic endo-lysosomes. The biomimetic MOF system needed minimum dosage of the therapeutic proteins and showed good cancer therapy. This was a significant platform for other therapeutic proteins leading to clinic applications of the protein-based nanomaterial.

## (2) Antigen and Antibody

Cancer immunotherapy-based antibodies and/or antigens are important in cancer treatment [94-100]. Nano-carrier gave vaccines more effective immune response than pure protein antibody/antigen [101, 102]. The antigen-presenting dendritic cells (DCs) can present the danger signal to T-lymphocyte and generating the CD<sub>4</sub><sup>+</sup> and CD<sub>8</sub><sup>+</sup> T cells, resulting of the cancer immunotherapy and induce the “immune memory” effect [103, 104]. The nano-carrier can “programming” the activation state of DCs and induce the cellular and humoral immunity [105]. In studies of antigen-induced immunotherapy, ovalbumin (OVA) is a common model antigen [106, 107]. In 2012, Irvine’s group used lipid-coated poly(lactic-co-glycolic acid) (PLGA) NPs as efficient carrier of OVA, and combined this with the adjuvant of the nano-vaccine to elicit three orders of magnitude higher serum anti-OVA IgG titers versus pure soluble OVA [108].

The biomaterialized MOF system is also a good potential carrier of the protein antigen as first described by Qu *et al* [109]. The OVA was encapsulated into the ZIF-8 NPs with a loading capacity of 7%, and then the

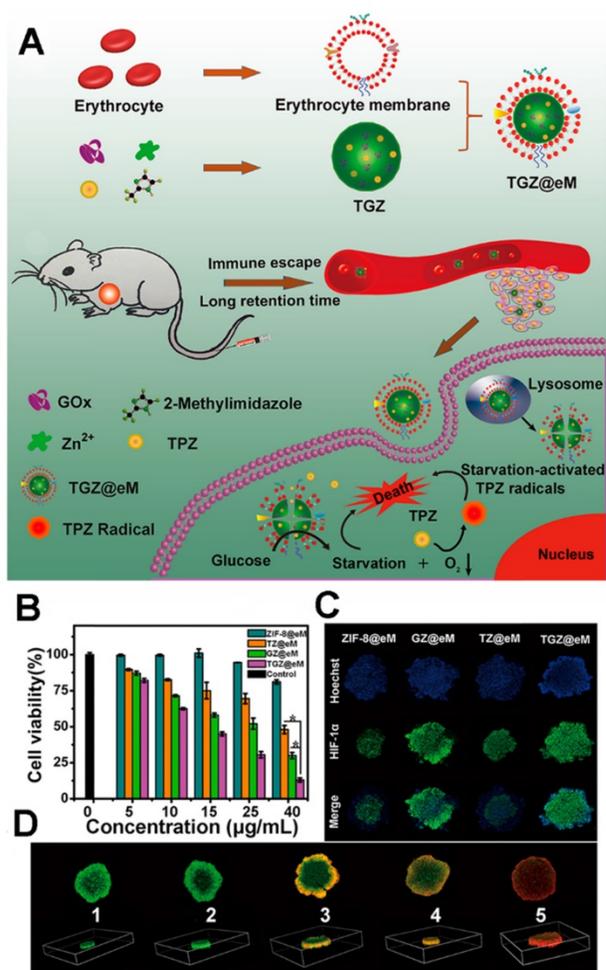
cytosine-phosphate-guanine oligodeoxynucleotides (CpG ODNs) was adsorbed on the surface of OVA@ZIF-8. Afterwards, in the group of RAW264.7 cells treated with OVA@ZIF-8-CPG, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interferon- $\gamma$  (IFN- $\gamma$ ) had much higher expression versus the other groups, implying the enhanced immunostimulatory activity of the nanocomposites. Later, an *in vivo* immune response of OVA@ZIF-8-CPG was studied after the nanocomposites subcutaneously injected into Kunming mice. The anti-OVA IgG titers were much higher than the OVA/CPG mixture. In addition, the CD<sub>4</sub><sup>+</sup> T and CD<sub>8</sub><sup>+</sup> T cells after OVA@ZIF-8-CPG treatment were also higher than the OVA/CPG mixture group. These results implied that the antigen-biomaterialized MOFs possessed superior loading capacity, efficient delivery, and pH-responsive release for antigen-presenting cells. This led to a strong humoral immune response. A good cancer immunotherapeutic effect was achieved by antigen-biomaterialized MOFs.

Moreover, tumors may evade immune destruction by endogenous “immune checkpoints” and terminate the antigen activated immune responses, the presence of immune inhibitory receptors in T cells [99]. So, the immune-checkpoint-pathway inhibitors such as anti-PD-L1 antibody, anti-PD1 antibody or anti-CTLA-4 antibody can recover the immune responses and develop cancer immunotherapeutic approaches [110-113]. The delivery of the antibody with an efficient strategy and controllable release of antibodies can spare the essential dose of the antibody and decrease the cost of treatment [114]. The antibody biomaterialized MOFs could protect the protein against various severe environment, we assume that the antibody biomaterialized MOFs can act as prominent delivery strategy of the immune-checkpoint-pathway inhibitors and feature powerful clinical potency in cancer immunotherapy.

## (3) Enzyme

For enzyme-induced cancer treatment, glucose oxidase (GOx) could catalyze glucose resulting in the production of gluconic acid and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) [115-117]. The rapid growth of the tumor was dependent on the glucose supply in the cancer cells, and the starvation therapy could eliminate tumors by the reduction of glucose *via* GOx [118-121]. In addition, as the hypoxia enhanced, the therapeutic effect of hypoxia-activated prodrugs could increase, and the synergy effect was achieved [122, 123]. Also, the generated H<sub>2</sub>O<sub>2</sub> could produce the hydroxyl radical through the Fenton reaction [124, 125], or oxidize L-Arginine (L-Arg) with a production of NO,

resulting of the starvation synergistic cancer therapy [126]. In recent years, the biomineralization of enzyme has been extensively investigated to enhance the enzymatic activity and extend the enzyme's application environment [42, 74, 127].



**Figure 4.** (A) Schematic illustration of the TGZ@eM and the cancer starvation therapy; (B) the cell viability after treated with different nanoparticles; (C) the HIF-1 $\alpha$  staining of MCTS after different treatments; (D) the fluorescence images of MCTS after treated with different nanoparticles ((1) PBS, (2) ZIF-8@eM, (3) GZ@eM, (4) TZ@eM, (5) TGZ@eM) [128]. Copyright 2018 American Chemical Society.

In 2018, Qu's group reported an enzyme@MOF hybrid for the starvation-activated therapy [128]. Through a self-assembly procedure (Figure 4), the GOx and prodrug tirapazamine (TPZ) were encapsulated in the ZIF-8 MOF, and the erythrocyte membrane was further coated on the surface of the MOF hybrid to enhance the tumor accumulation and blood circulation [129-136]. The loading amounts of GOx and TGZ were ~10 wt % and 13.2 wt% respectively, which were high enough for the further study. The GOx and TGZ were released into cytoplasm due to the acidity of the lysosome/endosome environment. The GOx could

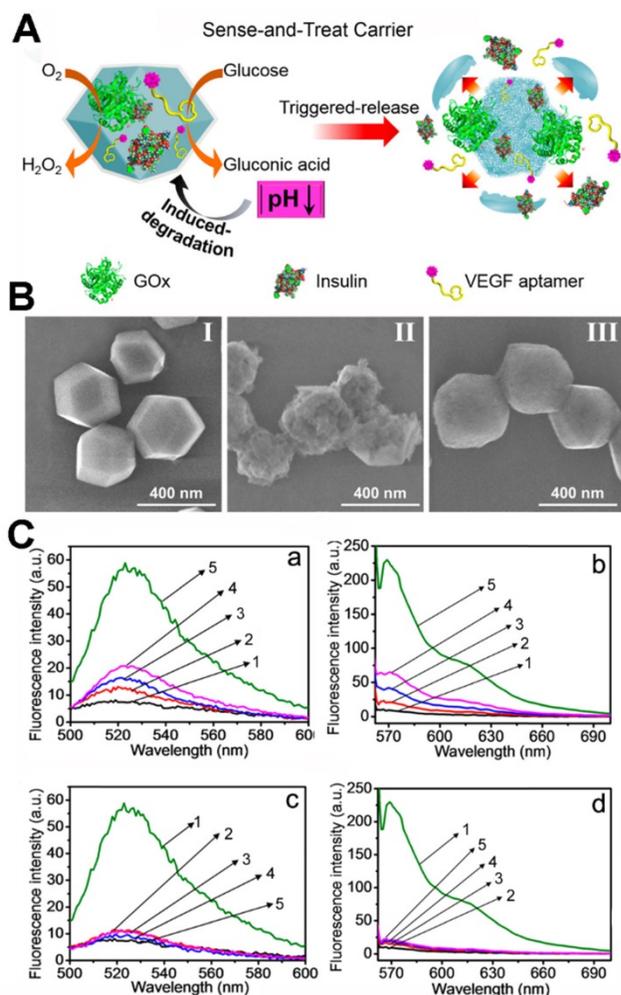
consume the endogenous glucose and O<sub>2</sub> to starve the cancer cells. Concurrently, a hypoxic microenvironment was enhanced and thus the TPZ was transformed into highly cytotoxic radical leading to synergistic therapy.

The TGZ@eM showed high cytotoxicity against CT26 cells than the other groups implying the combined treatment affect. The hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) staining assays of CT26 multicellular tumor spheroids (MCTS) after incubation with different nanostructures implied the O<sub>2</sub> reduction effect of GOx. A LIVE/DEAD kit was used after the TGZ@eM treatment to study cell cytotoxicity, and this was confirmed in the MCTS. The GOx in the TGZ@eM nanoreactor deprived the glucose and O<sub>2</sub> in the cancer cells resulting in starvation therapy and the hypoxia-induced chemotherapy. When studied *in vivo* of CT26 tumor-bearing mice, the TGZ@eM group showed satisfactory therapeutic outcomes, implying the synergistic effect of the GOx-based starvation therapy and the activated TPZ therapy.

Willner's group co-immobilized insulin/GOx or anti-vascular endothelial growth factor aptamer (VEGF aptamer)/GOx in ZIF-8 NPs (Figure 5) [137]. When the biomineralized MOFs were immersed in the glucose solution, the glucose was transformed to gluconic acid and the acidity of the solution increased. Afterwards, the ZIF-8 nano-mixture was decomposed, and the co-encapsulated insulin or VEGF aptamer was released. And, in the PBS (pH = 7.4), the ZIF-8 nano-mixture stained nanostructure without any change. In a further study, the release of insulin or VEGF was accelerated with the increasing of glucose concentrations. Glucose selectivity studies showed that only glucose could induce the release of insulin or VEGF. The glucose in angio-epithelial cells is higher than the normal cells [138-139], and the VEGF aptamer could inhibit the proliferation and migration of the epithelial cells [140-142]. Thus, the VEGF aptamer/GOx ZIF-8 NPs could respond in the epithelial cells, and the glucose was reduced along with release of the VEGF aptamer. The VEGF aptamer/GOx ZIF-8 NPs showed potential applications in cancer therapy. In the tumor tissues, the reduction of glucose by GOx might damage the cancer cells and epithelial cells via starvation; the released VEGF aptamer could inhibit angiogenesis.

Willner's group also demonstrated that two- or three enzyme cascades possessed better catalytic activity than the enzyme mixture in solution because the MOF nanoreactors provided the enzymes with intercommunication on the nanoscale [143]. The GOx and horseradish peroxidase (HRP) were encapsulated into ZIF-8 NMOFs, and the enzyme cascade was

activated with the addition of glucose. The biocatalytic activity of the obtained two-enzyme cascade was 7.5-fold enhanced than the GOx/HRP homogeneous mixture. The  $\beta$ -galactosidase ( $\beta$ -Gal)/GOx/HRP three-enzyme cascade was also evaluated, and the biocatalytic activity 5.3-fold enhanced than the  $\beta$ -Gal/GOx/HRP homogeneous mixture.



**Figure 5.** (A) The preparation procedure of the multifunctional GOx-loaded ZIF-8 MOFs and the glucose-responsive degradation procedure. (B) SEM images of insulin/GOx@MOFs (II), MOFs after reacted with glucose (50 mM) for 1 h (III) and MOFs incubated in PBS (pH 7.4) for 2 days. (C) Glucose-induced release from the insulin/GOx@MOFs (a) and VEGF aptamer/GOx@MOFs (b) in the presence of glucose ((1) 0 mM, (2) 1 mM, (3) 5 mM, (4) 10 mM, (5) 50 mM); selective glucose-induced release from the insulin/GOx@MOFs (c) and VEGF aptamer/GOx@MOFs (d) in the presence of glucose (1), galactose (2),  $\beta$ -lactose (3), sucrose (4), pure buffer solution (5) [137]. Copyright 2018 American Chemical Society.

MOFs that possessed stable nanostructure and enhanced enzyme catalytic activity in the endo-lysosome or cytoplasm might be another approach to the cancer treatment [144-148]. We assume that enzyme biomineralized MOFs can be applied to cancer therapy in two ways: (i) the enzyme-MOFs decompose in the tumor

microenvironment and thus the enzyme show catalytic effects combine with therapy of the other released drug (the MOFs decomposed due to the catalytic effect and the co-encapsulated drug was released); (ii) the enzyme-MOFs show enhanced catalytic effect in tumor tissues and influence the endo-biochemical system leading to the therapeutic effect.

### 3. MOFs-based biomineralization of DNA/RNA

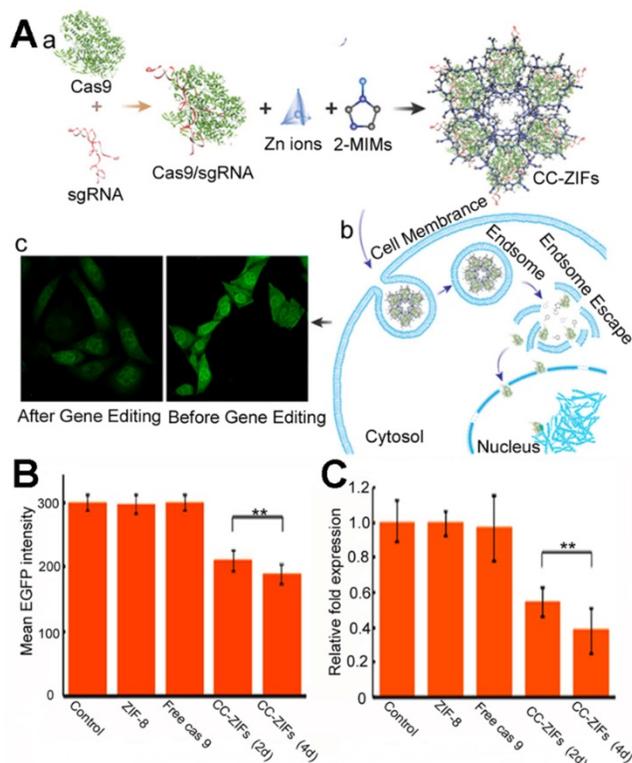
The cancer gene therapy based on the RNA or DNA has attracted significant attention in the past two decades [149-152]. The RNA interference (RNAi) has been applied to the sequence specific silencing of target messenger RNA (mRNA), and thus decrease the suppression of gene and protein, resulting of the gene therapy [153-154]. And, the synthetic short interfering RNAs (siRNAs) and plasmid DNA (pDNA) are the most widely studied therapeutic drugs for the RNAi [155]. However, these gene drugs are large biomacromolecules, cannot efficient delivered to the tumor tissues and cross the cell membrane to cytoplasm, and in the serum can be degraded by the nuclease. The current major strategies to delivery RNA or DNA are delivery nano-vehicles, including various cationic materials such as liposomal, polymeric formulations and inorganic nanoparticles [156]. There are some problems for these common delivery systems, such as suboptimal transfection effect and the potential hemolytic effect [157].

MOFs also can be applied in gene delivery system [158-159]. Mirkin and the other researchers recently prepared DNA-MOFs using click chemistry to conjugate the dibenzocyclooctyne-functionalized DNA (DNA-N3), azide-functionalized MOFs (MOFs-N3) [160,161], or coordination chemistry between the phosphate of DNA and the external metal nodes (Zr, Hf, Fe) of MOFs [162-164]. Lin and other researchers loaded the RNA on the surface of MOFs *via* metal ion connections or physical absorption [33, 164].

However, the complicated modification of DNA/RNA and the lack of release stimuli-environmental limit its application to gene therapy. Coating the DNA/RNA with non-toxic inorganic shells can leave out the DNA/RNA modification and extend the delivery system while keeping the length of the DNA/RNA unconstrained. In addition, the biomineralization can prolong the shelf life time and offer possibilities for clinical applications of genomic drugs [11].

Recently, calcium phosphate (CaP) has been used to coat living agents due to its good biocompatibility, stability, non-immunogenicity, and

pH-responsive decomposition in the tumor tissues [165]. And, the CaP can be used as the biomineral shells of the DNA/RNA *via* the interfacial interactions between calcium and phosphate ions, and the DNA/RNA can release due to the pH in the tumor cells [166, 167]. But the traditional biomineralization coating was critical to their surface, and direct biomineralization of the genetic macromolecules was difficult to realize. However, Liang *et al.* encapsulated DNA using ZIF-8 with a high encapsulation efficiency of 75% implying that the MOFs could be potentially applied as an effective bioactive DNA carrier [11].



**Figure 6.** (A) Biomimetic Cas9/sgRNA@MOF hybrid for genome editing: (a) schematic illustration of the Cas9/sgRNA encapsulated within ZIF-8; the Flow cytometry analysis (B) and qPCR quantitation (c) of different treatments 2 and 4 days [168]. Copyright 2018 American Chemical Society.

Khashab *et al.* first reported RNA-biomineralized MOFs [168]. The site-specific gene editing CRISPR/Cas9 platform was incorporated with a Cas9 protein and single guide RNA (sgRNA) for cancer treatment [169-171]. The co-delivery of the Cas9 protein or mRNA and sgRNA was necessary to translate this into the internal environment. To co-encapsulate the Cas9 protein and sgRNA, these authors encapsulated the CRISPR/Cas9 platform with ZIF-8 (Figure 6A) and the loading capacity was 1.2 wt% with an encapsulation efficiency of 17%. The pH-responsive nature of the ZIF-8 enabled the endosomal escape of the CRISPR/Cas9@ZIF-8 and the release of the gene editing platform. When the

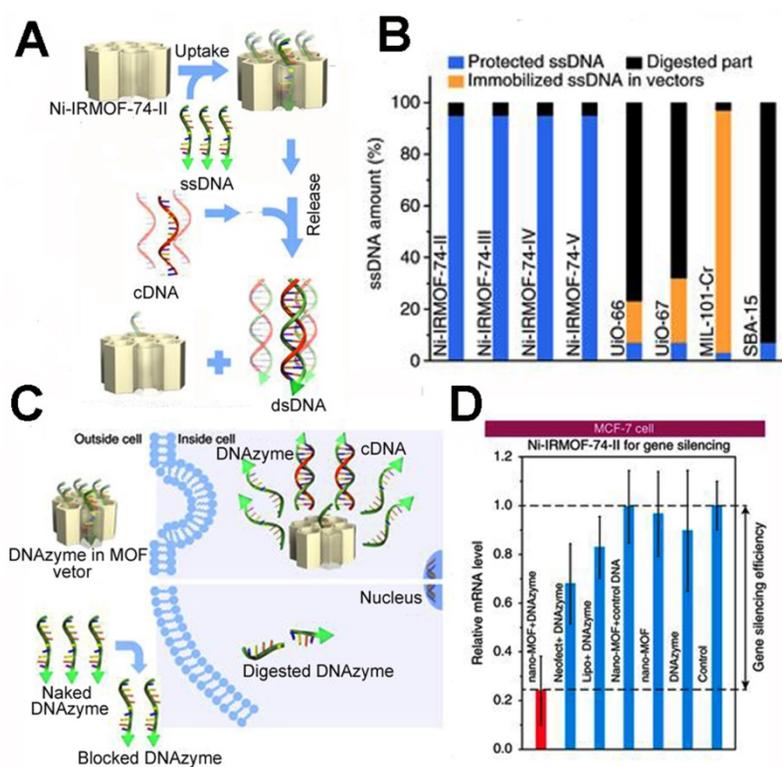
enhanced green fluorescent protein (eGFP) Chinese hamster ovary cells were treated with the eGFP editing CRISPR/Cas9@ZIF-8 nano-composites, the eGFP was reduced after 2 or 4 days, which was far more efficient than the free CRISPR/Cas9. The CRISPR/Cas9@ZIF-8 could also be potentially applied to cancer immunotherapy; this protein and RNA co-biomineralization strategy showed guidance for further RNA or protein-RNA delivery *via* MOFs.

Aside from the *in situ* biomineralization method, Zhou *et al.* presented a precise DNA loading method inner the isorecticular MOFs (NiIRMOF-74) [172]. By changing the length of the organic linker, the authors prepared NiIRMOF-74-II to -V with 2.2 to 4.2 nm pore sizes. The pore of the NiIRMOF-74 provided a host-guest interaction to the NiIRMOF-74 and single-stranded DNA (ssDNA). This enabled precise loading of the ssDNA inside the pores. Upon addition of the complementary DNA (cDNA), the ssDNA was released due to the interaction between the ssDNA and cDNA (Figure 7). The loading capacity was up to 6.9 wt%, which is far higher than other MOFs. The ssDNA loaded in NiIRMOF-74 could maintain 95% survival after incubation in FBS for 24 h, while the other porous nanostructures had low ssDNA survival, implying the good protection of NiIRMOF-74 vectors. When the MCF-7 cells were treated with 33-nucleotide ssDNA (DNAzyme)-loaded Ni-IRMOF-74-II, it inhibited 76% EGR-1 gene expression. The precise DNA loading rate and excellent transfection efficiency showed good potential in cancer gene therapy.

#### 4. Other biomineralization

Other than the biomacromolecule, various living bacteria and virus also have been applied in the cancer treatment. Even though the living bacteria and virus are promising in cancer treatment, sometimes the biomedical applications are limited by the host immune antiviral effect and inefficient tumor accumulation [173]. Artificial biomineralization of the living bacteria or virus agent can solve the problem of living agent-based cancer treatment [174]. By coating the living agent surface with a mineral layer or encapsulating several living agents into one mineral nanostructure, the living agent can accumulate in the tumor.

Biomineralization using CaP can be realized through the interactions between calcium ions and amino acids on the surface of the bacteria or virus, followed by the addition of phosphate ions [174, 175]. However, the certain amino acids on the surface of the living agents limited the universality for the strategy, and the morphology of the mineral hybrids need further study to meet the clinical research standard.



**Figure 7.** The precise inclusion of single-stranded DNA using isorecticular MOFs: (A) the ssDNA transfection procedure of ssDNA@Ni-IRMOF-74-II; (B) the protection studies of ssDNA using different porous nanostructures in FBS; (C) the intracellular delivery of ssDNA using ssDNA@Ni-IRMOF-74-II and pure ssDNA; (D) gene silencing efficiency of MCF-7 cells for the DNAzyme delivery with Ni-IRMOF-74-II, Lipo, and Neofec [172]. Copyright 2018 Nature.

As the core-shell nanostructure with MOF shell was studied, and combine with the study of the MOFs-based biomineralization, the various MOFs can also be applied in the biomineralization of the living agents.

### (1) Bacteria

Nowadays, the bacteria especially the *salmonella* has been applied as antitumor agents due to its tumor preferentially amplifying and even 1000 times than the normal tissues [176, 177]. The *salmonella* can express the prodrug-converting enzymes, such as herpes simplex thymidine kinase. In addition, the *salmonella* induces the production of the Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) from immune cells, and thus lead to the immune killing of cancer cell. With the development of the bacterial adjuvants, the applications of bacteria in the cancer treatment have gained much research interest [178-181].

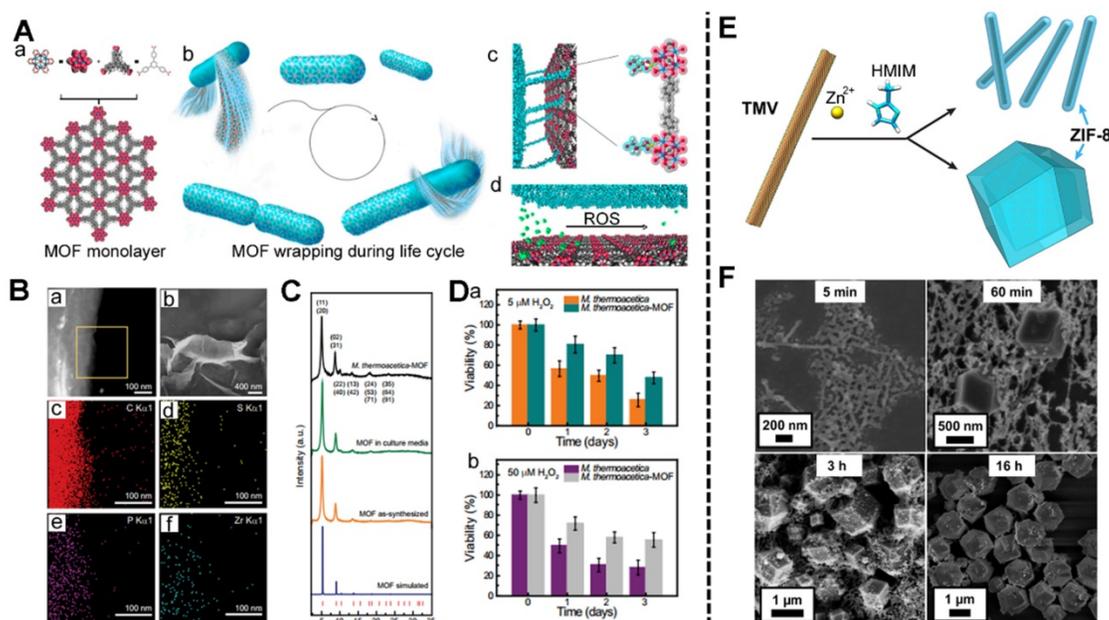
The Yang's group attempted the biomineralization of anaerobic bacteria using MOF based on the interaction between the  $Zr^{4+}$  and the phosphate units on surface of the bacteria [182]. As shown in **Figure 8**, the  $Zr_6O_4(OH)_4(BTB)_2(OH)_6(H_2O)_6$  clusters (BTB = 1,3,5-benzenetribenzoate) was coated on the surface of *Moorella thermoacetica* (*M. thermoacetica*) in all its life cycle. And, when treated with the ROS, the

viability of *M. thermoacetica*-MOF was obvious higher than the pure the *M. thermoacetica*, implying the good protection effect of the coated MOF shell. The efficient coating of the bacteria using MOFs and the protection effect could enable the application of the bacteria@MOFs in cancer treatment. In addition, with the rational design of the organic ligands, the bacteria@MOFs could be prepared to release in the tumor microenvironment or under the external excitation, and thus the bacteria showed therapeutic effect.

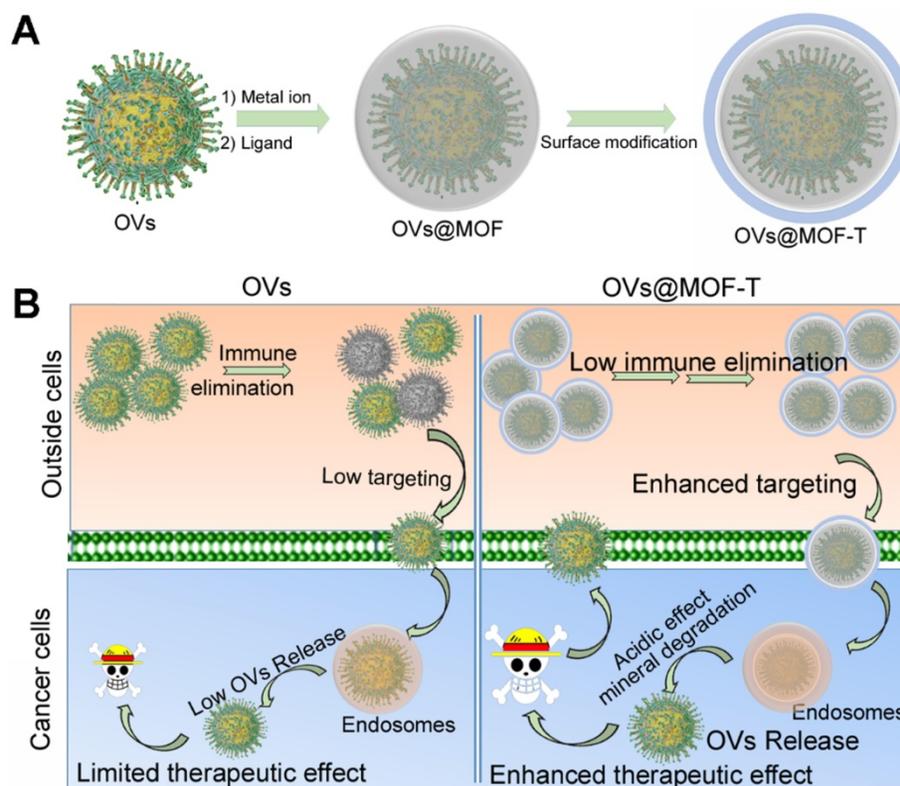
### (2) Virus

In addition, oncolytic viruses (OVs) including poxvirus, paramyxovirus, reovirus, and picornavirus are the most widely studied among virus immunotherapy [183, 184]. OVs are genetically modified to selectively infect the cancer cells and replicate in the cells regardless of the normal cells. The preclinical OVs have effective antitumor effect [185]. Viral gene delivery systems include adenoviruses (Ads) and lentiviruses. The Gassensmith's group used tobacco mosaic virus (TMV) as a template-fabricated TMV@MOF using ZIF-8 (**Figure 8E**) [44, 186-187]. The prepared TMV@MOF had a tuned nanostructure *via* changes in the synthetic conditions. Meanwhile, the surface of the TMV@MOF could also be conjugated with organic molecules or biomolecule *via* chemical reactions. Later, this group demonstrated that a high zinc concentration near the TMV could catalyze the growth of ZIF-8 on the surface of the TMV. This would benefit the other virus-MOF core-shell systems.

It was supposed that the OVs can be encapsulated into MOFs during direct self-assembly (**Figure 9**) [68]. And, the surface modification enhances the targeting effect and biocompatibility of the OVs@MOF. Unlike protein or DNA/RNA, the OVs are more difficult to store and transport. MOFs-based biomineralization gives the OVs@MOF a longer lifetime after assembly versus free OVs. In addition, the targeting modified OVs@MOF hybrid (OVs@MOF-T) is more suitable for cancer treatment. The OVs@MOF-T can specifically accumulate in the tumor tissues more efficiently regardless of the immunogenic effect of OVs. Subsequently, OVs are released from the endosomes due to the pH-response MOF disassembly, achieving significant therapeutic efficacy in cancer treatment.



**Figure 8.** The MOFs-based biomineralization of anaerobic bacteria: (A) the formation of the MOF (a), the *M. thermoacetica*–MOF wrapping cycle (b), the interface of the MOF and bacteria (c), the ROS response of the interface (d); (B) High-angle annular dark-field STEM image (a) and SEM image (b) of the prepared *M. thermoacetica*–MOF, EDS mapping of the *M. thermoacetica*–MOF ((c) C element, (d) S element, (e) P element, (f) Zr element); (C) PXRD pattern and Bragg position of *M. thermoacetica*–MOF, MOF soaked in culture media, MOF as-synthesized and MOF simulated; (D) The viability of *M. thermoacetica* and *M. thermoacetica*–MOF when treated with 5  $\mu\text{M}$  (a), and 50  $\mu\text{M}$  (b)  $\text{H}_2\text{O}_2$  [182]. Copyright 2018 National Academy of Sciences. The preparation of TMV@ZIF-8 nanocomposites: (E) the schematic illustration of the TMV@ZIF-8 rod-shaped nanocomposites; (F) the SEM of the TMV@ZIF-8 composites varying the reaction time. [187]. Copyright 2018 American Chemical Society.



**Figure 9.** The potential encapsulation procedure (A) and the intracellular delivery (B) of OV using MOF.

### 5. Conclusions and outlook

MOFs-based biomineralization is useful in biological catalysis or nanomedicine. The

biomineralization of protein, DNA/RNA, or viruses can be done with MOF encapsulation. Biotherapy for cancer with this approach has shown progress—the MOFs can be loaded with cancer-associated

biomacromolecules. The biomacromolecules maintain their biological activity regardless of the extreme tumor microenvironment and delivery *via* MOF protection.

For application of the biomineralization towards cancer therapy, the MOF should possess the following properties: (i) the MOF synthetic conditions should be moderately facile, and the MOF should interact with the biomacromolecules and protect them from the surroundings; (ii) the size, biological stability, and biosecurity of the MOF should meet the requirements for cancer treatment nanomedicine; (iii) the MOF should be responsive to the tumor microenvironment and thus the encapsulated biomacromolecules or living agents released. Currently, the preparation method for the MOFs-based biomineralization is mostly limited to the ZIF-8 or ZIF-90, and the organic bridging ligands still have *in vivo* toxicity. However, better understanding of nano-bio interactions to exploit MOF-architectures for cancer treatment can be adapted or modified to improve their performance and dose efficiency – this reduces patient exposure to the therapeutics.

In summary, the application of a MOF-biomineralized therapeutic protein, antigen/antibody, enzyme, and DNA/RNA leads to improved cancer treatment efficacy. Their properties allow for unique opportunities in modulating key components of the healthy organism system such as the inherent activation of immune cells and functional delivery of biomacromolecules as well as biosensing and monitoring of treatment response. The field of MOF-based cancer treatment combines researchers from multiple subdisciplines of material science, nano-chemistry, and nano-biological interactions, immunology, and medicinal chemistry. This leads to new opportunities to synergistically complement and improve MOF-based cancer nanomedicine.

## Acknowledgements

This work was supported by the Major State Basic Research Development Program of China (2017YFA0205201 and 2018YFA0107301), the National Natural Science Foundation of China (81422023, 81603015, 81871404, U1705281, and U1505221), the Fundamental Research Funds for the Central Universities (20720160065 and 20720150141), the Program for New Century Excellent Talents in University, China (NCET-13-0502) and Postdoctoral International Exchange Program [2012]310.

## Competing Interests

The authors have declared that no competing interest exists.

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