

# Atom-engineered metabzymes for catalytic metabolic regulation-augmented immunotherapy

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Cancer remains a significant global public health challenge. While standard treatment strategies, such as surgical resection combined with chemotherapy, typically lead to primary tumor shrinkage, these initial responses are often followed by recurrence. Over the past decade, cancer immunotherapy has emerged as a promising treatment modality.<sup>1</sup> However, clinical observations suggest that only a subset of patients benefit from durable immune responses,<sup>2</sup> highlighting the pressing need for novel strategies to enhance immunotherapy efficacy.

The tumor metabolic milieu, composed of both tumor and immune cells, is characterized by the Warburg effect, lactic acid accumulation, and dysregulated lipid metabolism, among other alterations. These metabolic disturbances impair immune cell function and contribute to the development of an immunosuppressive tumor microenvironment (TME).<sup>3</sup> In this context, small-molecule and oligonucleotide-based metabolic modulators have shown therapeutic potential.<sup>4</sup> However, current metabolic intervention agents frequently lack specificity in distinguishing neoplastic cells, resulting in unpredictable off-target effects and transient therapeutic efficacy in clinical applications.<sup>5</sup> As endogenous enzymatic entities, natural enzymes play a central role in regulating biochemical flux within the TME by mediating substrate-to-product biotransformation.<sup>6</sup> Compared with these natural enzymes, enzyme-like nanocatalysts, known as nanozymes, offer distinct advantages, including lower cost, enhanced stability, and prolonged preservation. These include peroxidase-, catalase-, and superoxide dismutase-mimicking nanozymes, among others.<sup>7</sup> Unfortunately, the rational design of multimetallic nanozymes with metabolic enzyme-like characteristics for tumor-specific metabolic modulation remains a formidable challenge, particularly with respect to optimizing catalytic activities at the atomic level to enhance immune efficacy.

artificial metabzyme, the first metabolic enzyme-like nanocatalyst, termed FeMoO<sub>4</sub>, which mimics the catalytic activity of xanthine oxidoreductase (XOR) to facilitate the conversion of xanthine to uric acid (UA) within tumor cells. The Fe/Mo bimetallic composites are engineered through stoichiometric co-assembly (Fe: Mo = 1:1) within oxygen-deficient molybdenum oxide matrices, undergoing coordinated structural evolution into a tetrahedrally coordinated architecture. This structural transformation enables the establishment of exclusive XOR-like catalytic functionality with optimized efficiency. In XOR-deficient tumor regions, FeMoO<sub>4</sub> nanozymes autonomously catalyze the conversion of xanthine to UA, leading to pathological-level urate overproduction. Notably, this precise metabolic regulation accelerates interleukin-1 $\beta$  (IL-1 $\beta$ ) secretion by macrophages, promoting M1 reprogramming and activating other immune cells. This approach represents a promising strategy for intercellular metabolic crosstalk between immune and tumor cells, facilitating tumor-targeted metabolic therapy.

The FeMoO<sub>4</sub> nanozyme is synthesized through a distinctive corrosion-adsorption-immobilization method. Initially, MoO<sub>3-x</sub> is obtained through hydrothermal treatment of MoO<sub>3</sub>. Subsequently, ferric acetylacetonate is introduced to incorporate Fe atoms into the MoO<sub>3-x</sub> structure. Density functional theory calculations reveal that the atomic doping process induces local structural and crystal phase transformations, which are crucial for establishing active sites for XOR-like catalysis. Mo vacancies serve as anchor points for Fe atom immobilization, resulting in the formation of tetrahedral Mo<sup>4+</sup> centers, which are essential for the catalytic activity of the nanozyme. Furthermore, the Fe-driven catalytic efficiency was validated by the high electron transfer rate and the structural similarity of the catalytic sites to Mo- and Fe-based XOR enzymes.

The FeMoO<sub>4</sub> metabzyme has demonstrated considerable potential in B16 melanoma cells by

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## Atom-engineered metabzymes for immunotherapy

catalyzing the conversion of xanthine to UA. Furthermore, FeMoO<sub>4</sub>-treated B16 cells stimulated IL-1 $\beta$  secretion and activated NOD-like receptors containing pyrin domain 3 (NLRP3) in RAW264.7 macrophages. These results suggest the activation of the UA-NLRP3-IL-1 $\beta$  signaling pathway, underscoring the role of FeMoO<sub>4</sub> in facilitating intercellular metabolic communication with macrophages to enhance the anti-tumor immune response. *In vivo*, FeMoO<sub>4</sub> metabzyme treatment resulted in significantly higher intratumoral UA levels compared to paracarcinoma muscle tissue. Spatial metabolite mapping of B16 tumor tissue revealed that regions with high-intensity UA signals coincided with FeMoO<sub>4</sub> localization, providing direct evidence of FeMoO<sub>4</sub>-mediated xanthine metabolism in tumor cells and establishing a foundation for cancer metabolic therapy. Simultaneously, this treatment upregulated the intratumoral levels of IL-1 $\beta$ , tumor necrosis factor- $\alpha$ , and IL-12p70, all of which are indicators of an anti-tumor immune response. Cytometry by the time of flight analysis further demonstrated that FeMoO<sub>4</sub> metabzyme treatment induced a favorable shift in the tumor immune landscape, increasing the M1/M2 macrophage ratio, and enhancing intratumoral infiltration of CD8<sup>+</sup> T cells, CD4<sup>+</sup> T cells, and natural killer cells. Meanwhile, the number of myeloid-derived suppressor cells decreased, whereas the population of mature dendritic cells increased. Furthermore, the combination of FeMoO<sub>4</sub> metabzyme with anti-programmed cell death 1 antibody therapy significantly enhanced therapeutic efficacy, resulting in notable tumor growth inhibition and prolonged survival in tumor-bearing mice.

In summary, this work has developed an artificial metabzyme, FeMoO<sub>4</sub>, for tumor-specific metabolic immunotherapy. By incorporating Fe atoms into MoO<sub>3-x</sub> to mimic the catalytic center of XOR, FeMoO<sub>4</sub> facilitates the conversion of xanthine to UA in tumor cells, inducing metabolic reprogramming that enhances immune responses. The unique corrosion-adsorption-immobilization synthesis method provides a platform for developing nanozymes with atomic-level architectural control. The meticulously designed FeMoO<sub>4</sub> nanozyme facilitates intercellular metabolic crosstalk with macrophages through the UA-NLRP3-IL-1 $\beta$  axis, effectively regulating immune cell fate and activating immune responses. By integrating atomic-level catalytic precision with intracellular biomedical interactions, FeMoO<sub>4</sub> paves the way for next-generation metabolic modulation-based therapies. However, despite the significant advances in nanozyme-based cancer therapy and inflammatory disease treatment, several intrinsic challenges persist, including potential metal-induced toxicity, off-target effects, and suboptimal therapeutic efficiency. The artificial metabzyme developed in this work lays the groundwork for targeted therapies that precisely modulate pathological immune responses within the TME, providing a specific paradigm for tumor-specific metabolic immunotherapy.

Despite the promising findings of FeMoO<sub>4</sub> in tumor-specific metabolic immunotherapy, several limitations should be acknowledged. First, the study primarily focuses on melanoma models, and the efficacy of FeMoO<sub>4</sub> in other tumor types with distinct metabolic landscapes remains to be explored. Second,

while FeMoO<sub>4</sub> demonstrates potent catalytic activity *in vitro* and *in vivo*, its long-term biocompatibility, biodistribution, and potential systemic toxicity remain unclear. Comprehensive pharmacokinetic and toxicological studies are essential to establish its safety profile. Third, the efficacy of FeMoO<sub>4</sub>-mediated immune modulation may not be significantly superior to that of gene-edited nanozymes. Future studies should focus on refining the nanozyme's design to improve tumor selectivity, catalytic efficiency, and immune activation while minimizing potential adverse effects. Addressing these challenges will be crucial for the clinical translation of FeMoO<sub>4</sub>-based metabolic immunotherapy.

**Author contributions**

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The authors declare no competing interest.

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