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Catalytic radiopharmaceuticals unlock immune memory by rewiring tumor metabolism

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In a recent issue of Military Medical Research, Yang et al. report a catalytic radiopharmaceutical that integrates radionuclide therapy with metabolic disruption and innate immune activation.[1] By amplifying reactive oxygen species (ROS) and inducing ferroptosis, this platform eradicates local tumors and establishes systemic immune memory, advancing oncology and military medicine.

Cancer is one of medicine's greatest challenges because it is diverse, adaptable, often able to escape both standard treatments and the body's immune system. One emerging strategy to address these challenges is targeted radionuclide therapy (TRT), a clinically validated precision oncology approach that delivers ionizing radiation selectively to tumors while sparing healthy tissues. Among available radionuclides, iodine-131 (^{131}I) is widely used owing to its favorable half-life, established production, and proven track record.[2] Yet, the broader application of TRT across solid tumors remains limited. Hypoxia suppresses radiation-induced DNA damage by diminishing ROS generation, while elevated glutathione (GSH) and lipid metabolism reprogramming buffer oxidative stress. At the same time, the immunosuppressive tumor microenvironment (TME) restricts immune effector cell activity, enabling tumors to remain "cold" despite radiation-induced damage.[3] Ferroptosis, a regulated form of cell death driven by iron-dependent lipid peroxidation, has recently emerged as a promising therapeutic avenue to overcome these resistance mechanisms.[4] These factors expose a critical problem in the field: the inability of conventional TRT to overcome redox homeostasis and metabolic plasticity that shield tumors from both radiotoxicity and immune surveillance. Addressing this challenge requires strategies that extend beyond radionuclide delivery to directly remodel tumor metabolism and reprogram immune interactions.

Recent research has turned to nanotechnology and biomimicry to address these barriers. Nanozymes, particularly single-atom nanozymes (SAEs), provide atomically dispersed catalytic centers capable of oxygen generation, ROS amplification, and GSH depletion, thereby alleviating hypoxia and collapsing antioxidant defenses. Cloaking nanoparticles with a cancer cell membrane (CCM) delivers a powerful triple effect: it drives homotypic recognition, unlocks immune evasion, and improves accumulation at the tumor site.[5] More broadly, this work reflects a growing convergence in cancer nanomedicine, where radiopharmaceuticals, catalytic nanoplatforms, and immuno-oncology strategies are being integrated to overcome metabolic and immune resistance. Recent advances in α-emitter-based theranostics, ferroptosis-targeting strategies, and nanomedicine-driven STING: Stimulator of interferon genes (STING) activation further highlight the broader effort to integrate metabolic and immune interventions in cancer therapy. Within this emerging landscape, catalytic radiopharmaceuticals represent a shift from single-modality treatment toward coordinated metabolic and immune reprogramming. The power of these design principles was demonstrated in a recent study published in *Military Medical Research*, where Yang et al. systematically engineered a single platform that integrates radionuclide therapy with catalytic metabolism disruption and immune activation [1]. By converging multiple therapeutic axes into a single platform, they highlight a path toward catalytic radiopharmaceuticals that not only eradicate tumors but also reprogram tumor metabolism and immunity for durable clinical benefit (Figure1).

Central to this study was the development of a nanoconstruct, named ^{131}I-Mn/SAE@M and the demonstration that it achieves catalytic radiopharmaceutical activity at the single-atom scale. The construct combines a Mn single-atom enzyme embedded in a Zeolitic imidazolate framework-8 (ZIF-8) scaffold, homologous CCM camouflage, and β-emitting ^{131}I labeling. The rationale is clear: to simultaneously amplify radiotoxic ROS, destabilize lipid homeostasis to induce ferroptosis, and release immunogenic signals that activate Cyclic GMP-AMP synthase (cGAS)-STING innate immunity. High-resolution imaging confirmed atomically dispersed Mn-N_x sites with mixed valences, which served as catalytic centers. These sites relieved hypoxia by generating O_2, amplified ROS through oxidase and peroxidase activity, and weakened redox defenses by oxidizing GSH. CCM camouflage nearly doubled cellular uptake, while radiolabeling preserved high purity and stability. The innovative design translated directly into powerful biology. The construct synergistically amplified ROS and β-emission to drive robust late apoptosis, while also inducing a metabolic collapse. This collapse bore the hallmarks of ferroptosis, reflected in reduced Hypoxia-inducible factor-1α (HIF-1α), suppressed Glutathione peroxidase 4 (GPX4), and extensive lipid remodeling across 48 classes and 3,308 species, including phospholipid loss and triglyceride buildup.

What makes this study particularly compelling is the *in vivo* validation, which shows that catalytic radiopharmaceuticals can both eradicate local tumors and awaken systemic immune memory. Single-photon emission computed tomography/Computed tomography (SPECT/CT) imaging confirmed selective tumor accumulation with minimal toxicity, leading to profound growth inhibition and suppression of distant, untreated tumors. Histology revealed extensive apoptosis, while oxidative damage triggered immunogenic cell death signals, including calreticulin exposure, High mobility group box 1 (HMGB1) release, and Adenosine triphosphate (ATP) secretion. These cues activated the cGAS-STING pathway and reshaped the tumor immune landscape, driving dendritic cell maturation, $CD8^+$ T-cell infiltration, and M1 macrophage polarization, alongside suppression of Regulatory T cells (Tregs) and Myeloid-derived suppressor cells (MDSCs). Strikingly, treating a primary lesion also suppressed the growth of distant, untreated tumors and established durable $CD8^+$ T-cell memory. These findings highlight how ^{131}I-Mn/SAE@M goes beyond conventional TRT by combining hypoxia relief, ferroptosis induction, and innate immune activation to deliver both local control and systemic protection.

Yang et al. provide a compelling proof-of-concept that catalytic radiopharmaceuticals can reprogram tumor metabolism and modulate innate immunity, which sets an inspiring foundation for the field. Their work raises exciting questions that open new avenues for exploration. While Yang et al. show both ferroptosis induction and activation of the cGAS–STING pathway, a direct causal link between these processes has not yet been established. The proposed mechanisms, such as DNA release or oxidized lipid signaling, should therefore be considered plausible but not yet experimentally confirmed. Identifying the key immunogenic signals that connect ferroptosis to cGAS–STING activation remains an important next step. Similarly, although lipidomics revealed extensive remodeling, yet the specific danger-associated lipid species that act as triggers are still unknown. Knockout or inhibitor models targeting GPX4, cGAS, and STING, together with high-resolution immune profiling of dendritic cells and T lymphocytes, could help clarify how metabolic collapse translates into durable adaptive immunity. Extending this elegant platform to metabolically diverse cancers and patient-derived xenografts will also test its generalizability and determine whether lipid interference can consistently convert immune "cold" tumors into "hot" ones. These findings suggest a broader framework in which metabolic

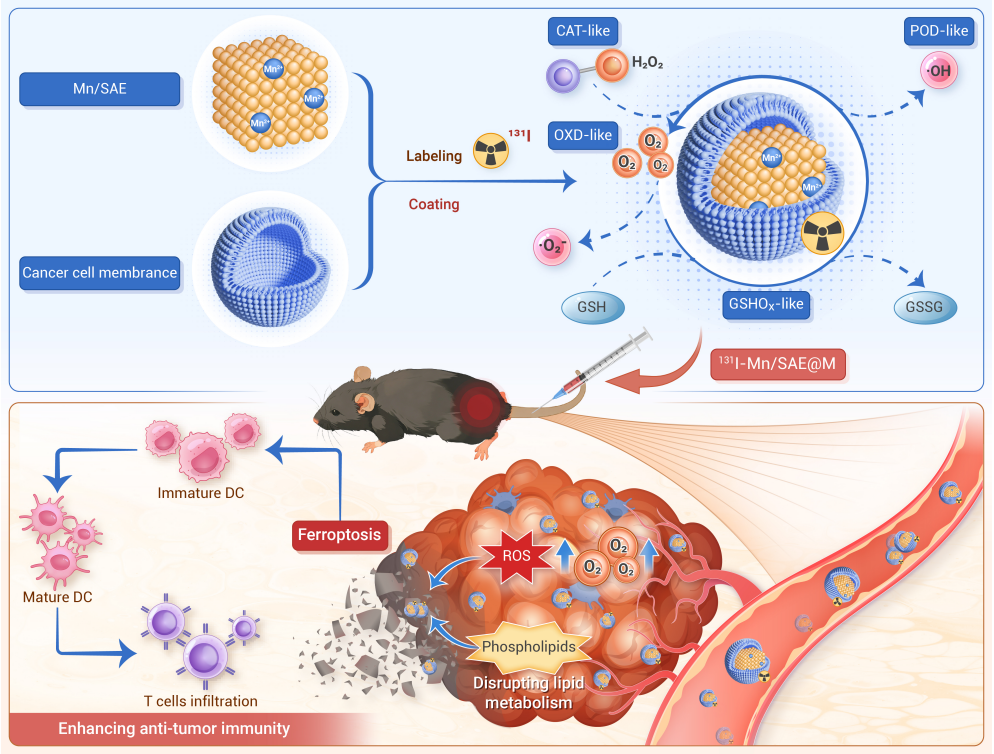

Figure 1. Schematic diagram of the construction of ^{131}I-Mn/SAE@M and its mechanism in disrupting tumor lipid metabolism and remodeling the tumor immune microenvironment This figure depicts the preparation and mechanism of ^{131}I-Mn/SAE@M, in which a cancer cell membrane-coated manganese single-atom nanozyme (Mn/SAE@M) serves as a carrier for delivering the radioactive isotope ^{131}I. The resulting nanostructure exhibits excellent tumor-targeting capability and efficient membrane camouflage-mediated cellular internalization. Within the tumor microenvironment (TME), β radiation emitted from ^{131}I triggers catalase (CAT)-like catalytic reactions to generate oxygen (O_2), alleviating tumor hypoxia. Meanwhile, Mn single-atom sites display oxidase (OXD), peroxidase (POD), and glutathione oxidase (GSHOx)-like activities, amplifying the production of reactive oxygen species (ROS). The excessive ROS disrupt lipid metabolic homeostasis, induce ferroptosis, and initiate immunogenic cell death signals, thereby promoting dendritic cell (DC) maturation and $CD8^+$ T-cell infiltration. Consequently, the ^{131}I-Mn/SAE@M nanoplatform remodels the tumor immune microenvironment and enhances antitumor immune responses.

disruption actively drives immune activation rather than simply reflecting cytotoxic stress. From this perspective, future strategies may benefit from engineering metabolic-immune coupling to convert tumor-intrinsic stress into durable antitumor immunity.

From a translational perspective, Yang et al. highlight both the promise and the challenges ahead. Scalable synthesis, CCM stability, and safe radionuclide handling remain key challenges. Beyond these considerations, potential off-target radiation exposure to normal tissues and the long-term biocompatibility of single-atom nanozymes remain critical concerns. In particular, nonspecific radionuclide accumulation and the uncertain biodistribution, persistence, and catalytic reactivity of metal-based nanozymes may pose risks of cumulative toxicity and unintended oxidative damage, warranting rigorous long-term evaluation. Despite these advances, the increasing complexity of such multifunctional systems may present challenges for clinical translation, particularly when compared with simpler ferroptosis-inducing agents or direct STING agonists currently under development. Compared with existing radiopharmaceuticals and nanozyme-based systems, this platform integrates catalytic amplification with homologous targeting and immune activation, but its added structural complexity may present challenges for scalability and controllability relative to simpler designs. In addition, the robustness of current preclinical evidence, largely derived from limited models and controlled settings, warrants cautious interpretation when considering reproducibility and broader clinical applicability. Future progress will likely depend on simplifying design while preserving functional synergy, and on defining which mechanistic components are truly essential for therapeutic efficacy. Large-animal pharmacokinetic and biodistribution studies will be essential to move this platform closer to the clinic. At the same time, the modular design invites innovation, whether by tailoring catalytic centers to other metabolic pathways or by integrating α-emitters and immune checkpoint inhibitors. Future research could also test alternative delivery vehicles, such as liposomes, polymeric nanoparticles, or exosome-based carriers, to optimize pharmacokinetics, improve radionuclide retention, and expand versatility across cancer types. Incorporating stimuli-responsive systems (e.g., pH-, enzyme-, or light-triggered release) could provide spatiotemporal precision, while biomimetic coatings beyond tumor membranes like platelet or immune cell membranes may further refine targeting and immune interactions. Pairing catalytic radiopharmaceuticals with emerging immunotherapies, metabolic inhibitors, or even cancer vaccines could amplify both local and systemic responses.

Importantly, the demonstration of systemic and durable antitumor immunity has implications beyond oncology, with potential relevance in military medicine where personnel may face unique cancer risks from carcinogen exposure, radiation, or treatment barriers during deployment. Such platforms may be particularly advantageous in scenarios involving combined radiation exposure and traumatic injury, where simultaneous control of tumor progression and immune dysfunction is required. In addition, their ability to induce systemic and durable immunity may offer therapeutic resilience in resource-limited or extreme environments where repeated interventions are not feasible. Beyond the specific construct of ^{131}I-Mn/SAE@M, this study sets a broader framework in which catalytic radiopharmaceuticals leverage metabolic disruption to drive immune-based, durable cancer control.

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AUTHOR CONTRIBUTIONS

H.P. and Q.T.H.S. conceived the commentary. S.Y. and X.Z. conducted the literature search. H.P. and S.Y. wrote the initial manuscript and drew the figure. H.P. and Q.T.H.S. supervised the commentary. All authors contributed to critical revision and interpretation. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

Quazi T. H. Shubhra is an Editorial Board member of The Innovation Drug Discovery and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.