New nanoparticle developed for intravenous cancer immunotherapy

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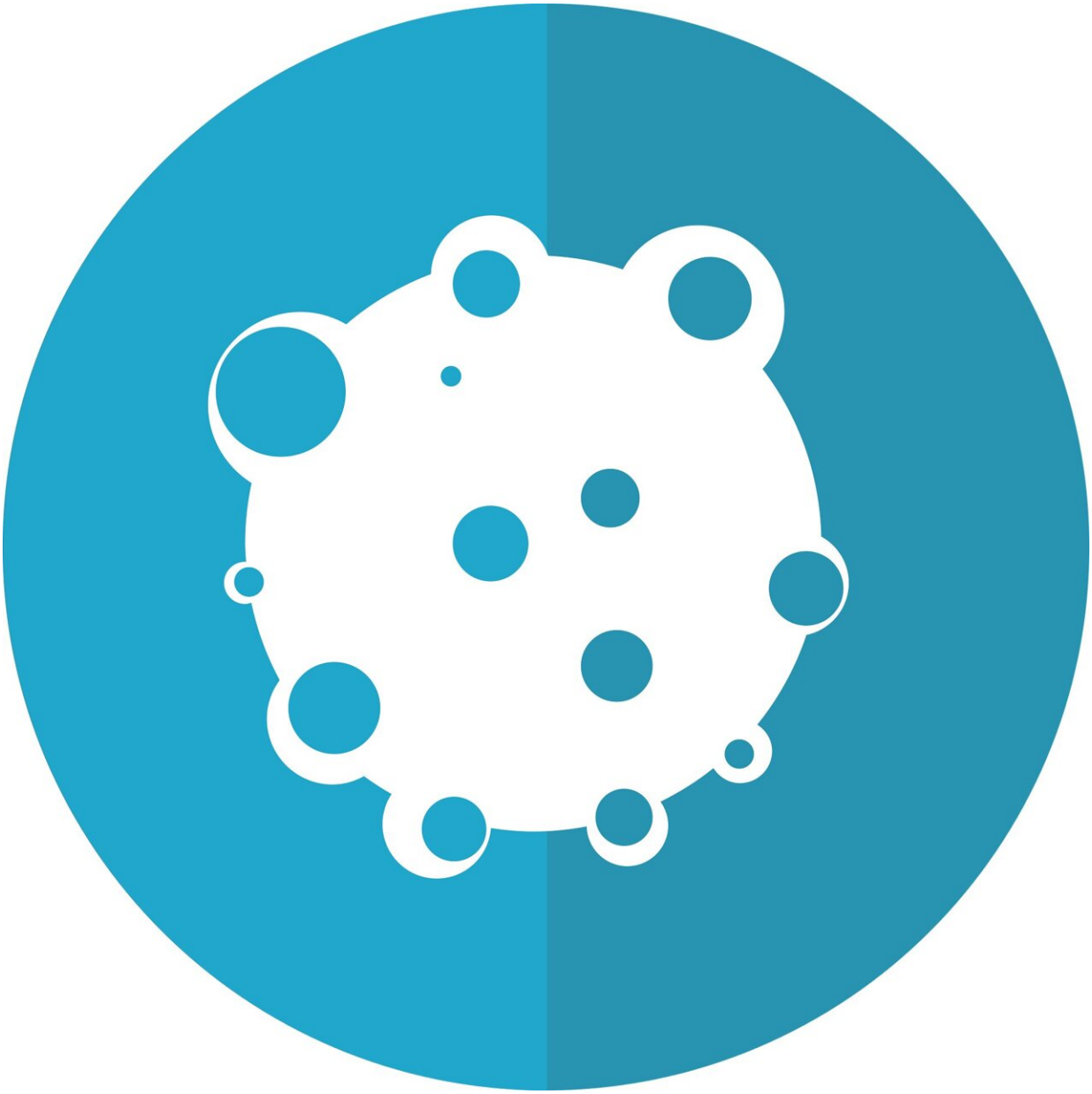

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Cancer immunotherapy seeks to turn "cold" tumors into "hot" tumors—those that respond to immunotherapy—by awakening and enlisting the body's own immune system.

Unfortunately, few people benefit from the most common form of immunotherapy, called immune checkpoint inhibitors, and scientists are actively seeking new and safe molecules called agonists to augment the body's immune response. One promising drug in clinical trials is the STING agonist. STING is a protein essential to the immune response against infection as well as cancer.

In searching for molecules that would augment the STING pathway, a team of scientists at the University of Michigan School of Pharmacy and the Rogel Cancer Center looked to nutritional metal ions, which we absorb from food, and are important for immune regulation.

They found that adding the nutritional metal ion manganese to STING agonists boosted STING's tumor-fighting capability up to 77-fold, compared to STING agonists used alone, said James Moon, the J.G. Searle Professor of Pharmaceutical Sciences and professor of biomedical engineering.

When researchers added the manganese ions to STING agonists, they formed nano-sized crystals, which significantly increased cellular uptake of STING agonists and STING activation by immune cells. To develop a STING agonist for intravenous administration, the researchers coated these nanocrystals with a lipid layer (similar to those found in mRNA COVID19 vaccines), resulting in a nanoparticle system called CMP.

Most STING agonists must be delivered directly into the tumor, but this isn't suitable for metastatic cancers, a major cause of mortality. Even with intratumoral injections, conventional STING agonists are challenged by limited clinical response.

"CMP significantly increases cellular uptake of STING agonists, and together with manganese, CMP triggers robust STING activation, turns a cold tumor into hot tumor, and eliminates cancer, including those that are completely resistant to immune checkpoint inhibitors, the most widely used cancer immunotherapy," said Xiaoqi "Kevin" Sun, a U-M graduate student in pharmacy and first author on the paper.

Moon said it's the first time that nanoparticles delivering STING agonists and metal ions have been developed for intravenous cancer immunotherapy, and this could open new doors for cancer immunotherapy treatments.

The team demonstrated the tumor-fighting effects of CMP in various tumors, including colon carcinoma, melanoma, and head and neck cancer.

Most head and neck cancers don't respond well to immune checkpoint inhibitors. To model this deadly disease, the team developed a head and neck cancer model that was completely resistant to immune checkpoint inhibitors, said study senior co-author Yu Leo Lei, U-M associate professor of dentistry. The model, called NOOC1, bears over 90% similarity in mutational signatures to smoking-associated human cancers.

"In the head and neck cancer tumor, CMP administered intravenously eradicated those tumors in 75% of mice," Lei said. "In contrast, conventional STING agonists had minimal anti-tumor effects and all animals succumbed to tumor growth."

The study team is currently working to test the safety and efficacy of CMP in large animals.

"We anticipate that we will be able to initiate a phase I clinical study to examine the efficacy of CMP in cancer patients in the near future," Moon said.

The research was published in *Nature Nanotechnology*.

More information: Sun, X. et al, Amplifying STING activation by cyclic dinucleotide–manganese particles for local and systemic cancer metalloimmunotherapy, *Nat. Nanotechnol.* (2021). doi.org/10.1038/s41565-021-00962-9

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