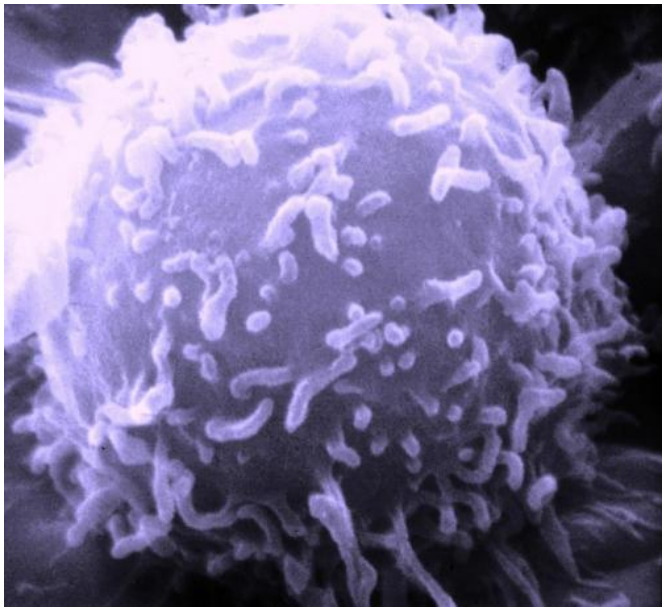
New nanotechology design provides hope for personalized vaccination for treating cancer

2 October 2020



Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

One of the key challenges in developing effective, targeted cancer treatments is the heterogeneity of the cancer cells themselves. This variation makes it difficult for the immune system to recognize, respond to and actively fight against tumors. Now, however, new advances in nanotechnology are making it possible to deliver targeted, personalized "vaccines" to treat cancer.

A new study, published on October 2, 2020 in *Science Advances*, demonstrates the use of charged nanoscale metal-organic frameworks for generating free radicals using X-rays within tumor tissue to kill cancer cells directly. Furthermore, the same frameworks can be used for delivering immune signaling molecules known as PAMPs to activate the immune response against tumor cells.

By combining these two approaches into one easily administered "vaccine," this new technology may provide the key to better local and systemic treatment of difficult-to-treat cancers.

In a collaboration between the Lin Group in the University of Chicago Department of Chemistry and the Weichselbaum Lab at University of Chicago Medicine, the research team combined expertise from inorganic chemistry and cancer biology to tackle the challenging problem of properly targeting and activating an innate immune response against cancer. This work leveraged the unique properties of nanoscale metal-organic frameworks, or nMOFs—nanoscale structures built of repeating units in a lattice formation that are capable of infiltrating tumors.

These nMOFs can be irradiated with X-rays to generate high concentrations of free oxygen radicals, killing the cancer cells directly and producing antigens and inflammatory molecules that help the immune system recognize and clear cancerous cells, much like a vaccine. Their lattice-like structure also makes nMOFs ideal transporters for delivering anti-cancer drugs directly to tumors. Thus far, however, it has been difficult to activate innate and adaptive immune responses necessary for eliminating cancerous tumors.

In this new study, the researchers fine-tuned their approach even further. This time, they generated a new type of nMOF structure that could be loaded with drugs known as pathogen-associated molecular patterns, or PAMPs. Now, when the nMOFs were applied to cancerous tumors, irradiating the tissue had a double effect: it triggered the nMOFs to kill local cancer cells to produce antigens against the tumor and released the PAMPs, which then triggered a much stronger activation of the immune response to the tumor

antigens. This one-two punch was capable of killing both colon and pancreatic cancer cells with high efficacy, even in tumor models that are highly resistant to other kinds of immunotherapy.

In further experiments with mice, the investigators saw they could extend the effects of the nMOFs even to distant tumors with the application of checkpoint inhibitors, providing new hope for treating cancer both locally and systemically with this approach.

"By including PAMP delivery with the nMOFs, this is the first time we were able to really enhance the immune response to the antigens," said senior author Wenbin Lin, Ph.D., the James Franck Professor of Chemistry and a primary investigator of tumor immunology at the Ludwig Cancer Center at UChicago. "This is entirely different from all of our previous studies because we've shown that the nMOFs plus PAMPs can impact all of the aspects required for activating the immune system. We can use this nanoformulation to enable personalized cancer vaccinations that will work on any patient, because this strategy will not be subject to the heterogeneity we see among different patients."

The effects of the treatment were so pronounced that the researchers are eager to bring the technology to clinical trials, where other versions of the nMOF technology are already being tested, with promising results thus far.

"The brilliance of this system is twofold," said co-author Ralph Weichselbaum, MD, the Daniel K. Ludwig Distinguished Service Professor of Radiation and Cellular Oncology and Chair of the Department of Radiation and Cellular Oncology at UChicago. "First, it can improve local tumor control by increasing the killing power of X-rays. Second, while there has been interest in using radiation to stimulate the immune response to fight cancer, it has turned out to be harder than we thought. In this case, the nMOFs are able to activate the innate and adaptive immune systems, which makes this technology very promising for treating cancer in the clinic."

Already looking ahead to next steps, the investigators are working on refining the technology. "We're refining the design of the nMOF and its delivery of the PAMPs, in preparation for testing it in humans," said Lin. "We're really working on zooming in on the best formulation so we can get this into clinical trials, hopefully in the next two to three years, or even sooner."

The team credits the interdisciplinary and collaborative nature of UChicago and University of Chicago Medicine's Hyde Park campus for creating a space where chemistry and cancer biology have combined to produce such a promising potential therapy, as well as the support they've received from Ludwig Cancer Research along the way.

"From the conception of this project and getting it funded to starting with clinical trials where we're able to test the technology in clinical trials and get real patient data, this work has all been done right here at UChicago," said Weichselbaum. "We really are going from discovering something in the lab to testing it at the bedside."

More information: "Nanoscale metal-organic frameworks for x-ray activated in situ cancer vaccination" *Science Advances* (2020). advances.sciencemag.org/lookup … .1126/sciadv.abb5223

Provided by University of Chicago Medical Center