
Ludwig Chicago Nanotechnology Induces Therapeutic Immune Responses Against Multiple Types of Tumors in Preclinical Studies

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A Ludwig Cancer Research study has developed a novel nanotechnology that triggers potent therapeutic anti-tumor immune responses and demonstrated its efficacy in mouse models of multiple cancers.

Led by Co-director Ralph Weichselbaum, investigator Wenbin Lin and postdoctoral researcher Kaiting Yang at the [Ludwig Center at Chicago](#), the study describes the synthesis, mechanism of action and preclinical assessment of the nanoparticle, which is loaded with a drug that activates a protein central to the efficient induction of anti-cancer immunity. The study, which overcomes significant technical barriers to targeting that protein—stimulator of interferon genes, or STING—for cancer therapy, appears in the current issue of [Nature Nanotechnology](#).

“The nanoparticles developed by the Lin lab release a drug that targets macrophages and can activate potent antitumor immune responses that extend the survival of mice bearing a variety of tumors,” said Chicago Center Co-director Weichselbaum. “When used in combination with radiotherapy and immunotherapy, they even help control ‘cold tumors’ that are otherwise almost completely impervious to immune attack.”

STING is part of cellular sensing system for DNA fragments, which are generated by infection or cancer treatments that damage DNA, like radiotherapy and some chemotherapies. Its activation promotes inflammation and drives immune cells like macrophages and dendritic cells to process and present cancer antigens to T cells, helping to stimulate and direct the immune assault on tumors. Though STING is a prized target for drug development, the drug-like molecules that can activate the molecular sensor—known as cyclic dinucleotides (CDNs)—have been plagued by issues of poor bioavailability, low stability and high toxicity in the absence of any means to target them specifically to tumors.

To better target such drugs, Weichselbaum, Lin, Yang and colleagues encapsulated a type of CDN in self-assembling spherical particles called nanoscale coordination polymers. A single dose of the nanoparticles, called ZnCDA (owing to the zinc ions at their core), suppressed tumor growth in two mouse models of colon cancer: a subcutaneously injected solid tumor and a model of liver metastases. ZnCDA also extended survival in a model of B-cell lymphoma, suppressed tumors in melanoma and prostate cancer models and induced anti-tumor effects in a model of a type of lung cancer that resists STING activators.

Nanoparticles injected into the blood tend to accumulate in tumors because their malformed blood vessels are leaky and because tumors have poor drainage systems. However, the researchers noticed that ZnCDA gathered in tumors at levels too high to be attributable to passive accumulation alone.

“The accumulation of ZnCDA also activates STING in the cells that line tumor blood vessels, and this disrupts the tumor vasculature, increasing its leakiness and enhancing the accumulation of the nanoparticles,” said Lin. “In a sense, the nanoparticles drive their own delivery to malignant tissues, limiting toxicity and increasing the efficiency of drug delivery.”

Macrophages in tumors exist in a biological gradient between two states, or phenotypes: one, known as M1, in which they stimulate anti-tumor immune responses and attack cancer cells themselves—literally eating them up—or another (M2), in which they support cancer cell proliferation and survival.

“We found that ZnCDA is taken up particularly well by a subpopulation of macrophages in which it switches on gene expression programs that both push them toward the M1 state and promote their presentation of cancer antigens to T cells,” said Yang.

The researchers also tested the therapeutic potential of ZnCDA against two types of tumors, pancreatic cancer and glioblastoma. Both diseases are generally incurable and aggressive, characterized by cold tumors that resist radiotherapy and all existing immunotherapies.

The researchers found that, with ZnCDA treatment, a mouse model of pancreatic cancer became vulnerable to anti-PD-L1 immunotherapy, extending the survival of tumor-bearing mice. When radiotherapy was added to the regimen, the extension of survival was even more dramatic. The researchers also showed that ZnCDA could traverse the blood-brain barrier and accumulate in gliomas, where it drew T cells into tumors and, when combined with anti-PD-L1 immunotherapy, prolonged the survival of treated mice. Adding radiotherapy to the mix, once again, extended survival.

With proof-of-concept in hand, the researchers are now poised to translate this nanotechnology for future use in the clinic.

Read the [original article](#) on Ludwig Cancer Research.