New radiation-free targeted therapy detects and eliminates breast cancer tumors in mice

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Combining a compound known as a gallium corrole with a protein carrier results in a targeted cancer therapy that is able to detect and eliminate tumors in mice with seemingly fewer side effects than other breast-cancer treatments, says a team of researchers from the California Institute of Technology (Caltech), the Israel Institute of Technology (Technion) and the Cedars-Sinai Medical Center.

A paper describing their work is highlighted in this week's issue of the online edition of the Proceedings of the National Academy of Sciences (PNAS).

Corroles have very similar structures to the porphyrin molecules used in a well-studied cancer treatment known as photodynamic therapy, or PDT, in which porphyrin compounds injected into the body are exposed to specific wavelengths of laser light. The light prompts the porphyrins to produce active, tumor-killing oxygen radicals.

The difference between porphyrins and corroles, says Harry Gray, Caltech's Arnold O. Beckman Professor of Chemistry and founding director of the Beckman Institute, is that some corroles don't require a laser boost to turn lethal. "The striking thing about gallium corroles is that they apparently kill cancer cells in the dark," says Gray. "We don't yet know exactly how this works, but what we've seen so far tells us that it does work."

He notes that "ongoing work in our laboratories focuses on testing our

leading hypotheses for elucidating the mechanism of action."

In the experiments described in the *PNAS* paper, the team paired a gallium corrole with a carrier protein, then aimed it at cells that carry the human epidermal growth factor receptor 2 (HER2). The presence of a HER2 receptor is the hallmark of about 25 percent of breast cancers, and marks those tumors as particularly aggressive and difficult to treat.

In trials in mice, the targeted corrole was able to shrink tumors at doses five times lower than that of the standard chemotherapeutic agent for HER2-positive tumors, a drug called doxorubicin. In contrast with doxorubicin, the corrole was injected into the bloodstream, rather than directly into the tumor.

"We looked at three groups of mice with human tumors," explains paper coauthor Lali Medina-Kauwe, an assistant professor of medicine at the David Geffen School of Medicine at UCLA, and a faculty research scientist in the Department of Biomedical Science at Cedars-Sinai Medical Center in Los Angeles. "In one, we introduced just the protein carrier, without the corrole; tumor growth in those mice did not change. In other mice, we gave the corrole without the carrier protein; this led to some tumor suppression. But it was the last group, the ones that got the corrole with the carrier protein, that experienced the most therapeutic effect."

"The fact that we can target this compound means we can give it at very low concentrations," adds coauthor Daniel Farkas, director of Cedar-Sinai's Minimally Invasive Surgical Technologies Institute. "Using lower concentrations means less toxicity. Doxorubicin tends to have significant heart toxicity; this therapy seems likely to be much less damaging to the heart."

In addition, adds Medina-Kauwe, targeted compounds can seek out

tumors wherever they may be. "One of the beauties of targeting," she says, " is that we can go after metastatic tumors that are too small to be seen."

These targeted gallium corroles are not only effective, they're also easy to study, notes Zeev Gross, the Reba May & Robert D. Blum Academic Chair at Technion, the Israeli Institute of Technology, in Haifa, and another of the paper's coauthors. "In most cases, if people want to get a closer look at a drug in vivo, they have to attach a fluorescent probe to it--and that turns it into a different molecule. But in our case, the active molecule we're tracking does the fluorescing. We get to track the original, unmodified molecule and are hence able to follow its distribution among different organs in live animals."

The difficulty in getting to this point, notes Gray, is that corroles have been challenging to synthesize. "Then Zeev came up with a powerful synthetic method to make corroles," he says. "We went from being able to make a couple of milligrams in two years to being able to make two grams in two days. It really puts corroles on the map."

Gray and Gross further add, "It is truly fulfilling to see how the close collaboration between our research groups at Caltech and the Technion, which started 10 years ago with a focus on developing the fundamental science of corroles, led to pharmaceutical utility when we joined forces with Medina-Kauwe and Farkas, who are experts in cellular biology and biomedical imaging technologies."

More information: "Tumor detection and elimination by a targeted gallium corrole," *PNAS*.

Source: California Institute of Technology (news : web)