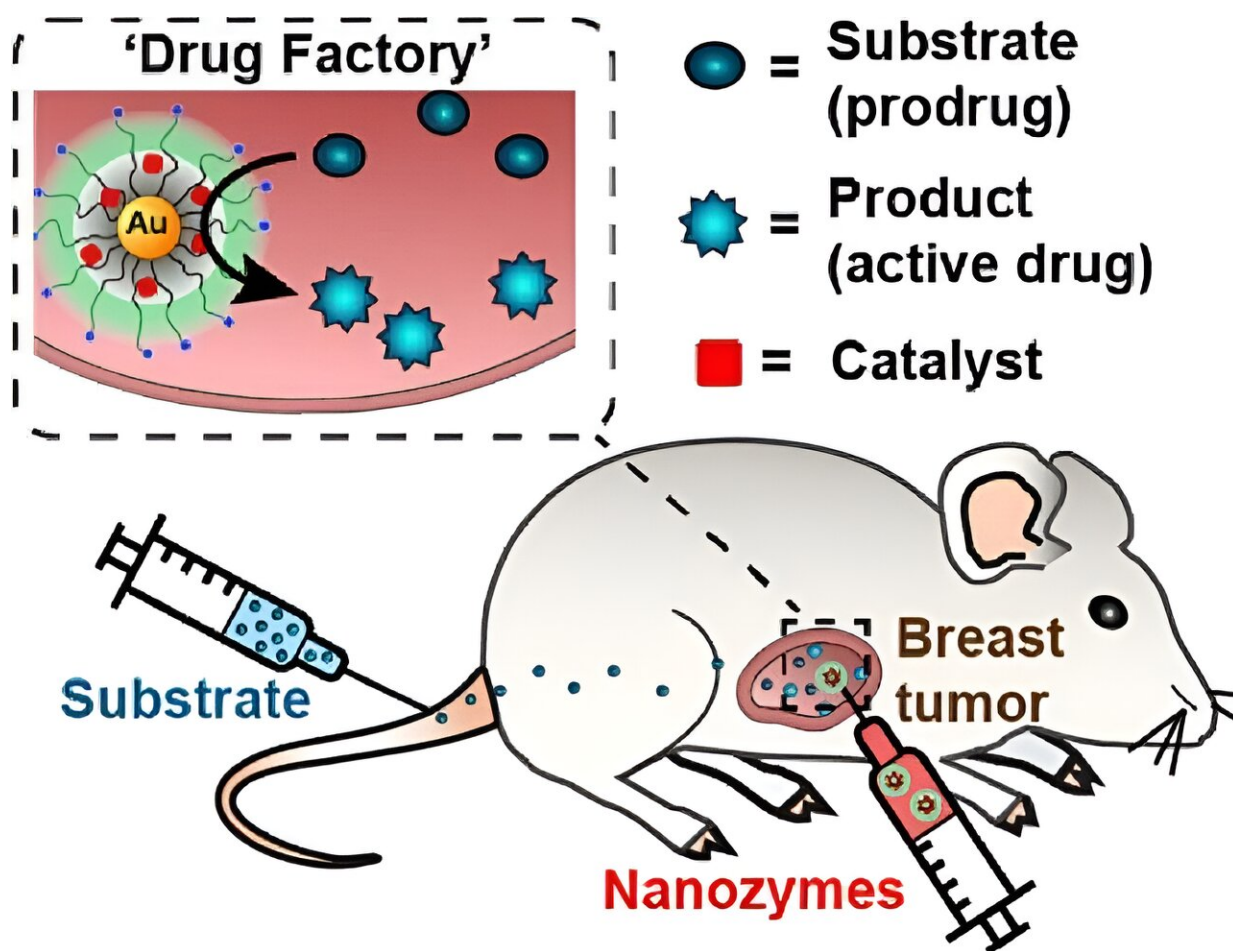


Nanozymes drive tumor-specific drug delivery while minimizing toxicity

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Graphical abstract. Credit: *Journal of Controlled Release* (2023). DOI: 10.1016/j.jconrel.2023.03.032

Chemotherapy is a mainstay of cancer treatment. While effective, this therapy indiscriminately kills rapidly dividing cells—cancerous or otherwise—so patients frequently experience severe side effects, ultimately limiting its utility.

But what if there was a way to administer an inactive chemotherapeutic throughout the body and 'turn on' the [drug](#) inside of a tumor? This strategy could limit side effects while potentially allowing for higher-dose (and more effective) treatments.

Enter nanozymes. These [artificial enzymes](#), composed of nanomaterials, can carry out pre-determined chemical reactions, such as converting an inert drug (or prodrug) into its functional form. If injected into a tumor and exposed to a prodrug, nanozymes could become localized 'drug factories,' selectively activating a cancer drug within the tumor while minimizing damage to healthy tissues.

Bioengineers and chemists at the University of Massachusetts Amherst (UMass Amherst) have developed a nanozyme that can turn an inactive form of fluorouracil, a commonly used chemotherapeutic, into its active form. When evaluated in a mouse model of breast cancer, their [treatment](#) could shrink tumors just as effectively as standard fluorouracil chemotherapy with significantly less liver damage.

By increasing chemotherapeutic doses at the tumor site and not throughout the body, this strategy could potentially provide just as much therapeutic benefit as standard chemotherapy with significantly less toxicity. Results from this method were recently reported in the *Journal of Controlled Release*.

"Developing targeted, safer therapies for cancer treatments will always be a major priority in the field," explained Luisa Russell, Ph.D., a program director in the Division of Discovery Science & Technology at

NIBIB. "This research demonstrates a way to make an existing chemotherapy less toxic without sacrificing efficacy in a preclinical model of breast cancer. Notably, this technique could potentially be applied to other types of drugs, paving the way for targeted treatments for a variety of different conditions."

Here's how the nanozymes are designed: ultrasmall gold nanoparticles are densely coated with positively charged molecules, making them strongly attracted to cell surfaces (which are negatively charged). Next, a [metal catalyst](#)—in this case, palladium—is added to the interior of the nanoparticles.

Palladium powers the activity of the nanozymes and can perform bio-orthogonal catalysis (reactions that don't naturally occur in our bodies). Specifically, palladium can remove molecules called propargyl groups, which can be added to drugs to block their activity.

"Metal catalysts, like palladium, are emerging as a new way to selectively activate prodrugs in [biological systems](#)," said senior study author Vincent Rotello, Ph.D., a professor of chemistry at UMass Amherst.

"By encapsulating palladium into our ultrasmall, positively charged nanoparticles, we can electrostatically 'velcro' the nanozymes to the tumor tissue, anchoring the catalyst in place," he explained. When a prodrug is added, it travels through the body but is activated within the tumor, improving therapeutic efficiency while also decreasing off-target effects, he added.

Their treatment combines the palladium-filled nanozymes with pro-fluorouracil (a version of the drug that is tagged with a propargyl group). After the nanozymes are injected directly into the tumors, mice are given pro-fluorouracil systemically (so that the drug circulates throughout the entire body). Once the drug travels to the [tumor](#), the

nanozymes cleave off the propargyl group, activating the chemotherapeutic which then kills the surrounding cells.

The researchers compared their nanozyme treatment with standard fluorouracil in mice with breast tumors. While both treatments markedly shrank the tumors, mice that were given standard fluorouracil experienced significantly more liver damage (which is the most common side effect of fluorouracil-based chemotherapy).

"Our [palladium](#)-filled nanozymes could potentially be used with any drug or compound whose activity can be blocked by adding a propargyl group," said Rotello. "We are generating chemotherapeutics, anti-microbials, and anti-inflammatories using this strategy." He also noted that other [metal catalysts](#) could be added into the nanozymes (which could perform different bio-orthogonal reactions that activate additional prodrugs).

"While our strategy will need some fine-tuning before it can be evaluated in humans, I believe that [nanozyme](#)-facilitated drug delivery could be a potential gamechanger for targeted, safer treatments."

More information: Xianzhi Zhang et al, Bioorthogonal nanozymes for breast cancer imaging and therapy, *Journal of Controlled Release* (2023). [DOI: 10.1016/j.jconrel.2023.03.032](https://doi.org/10.1016/j.jconrel.2023.03.032)

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