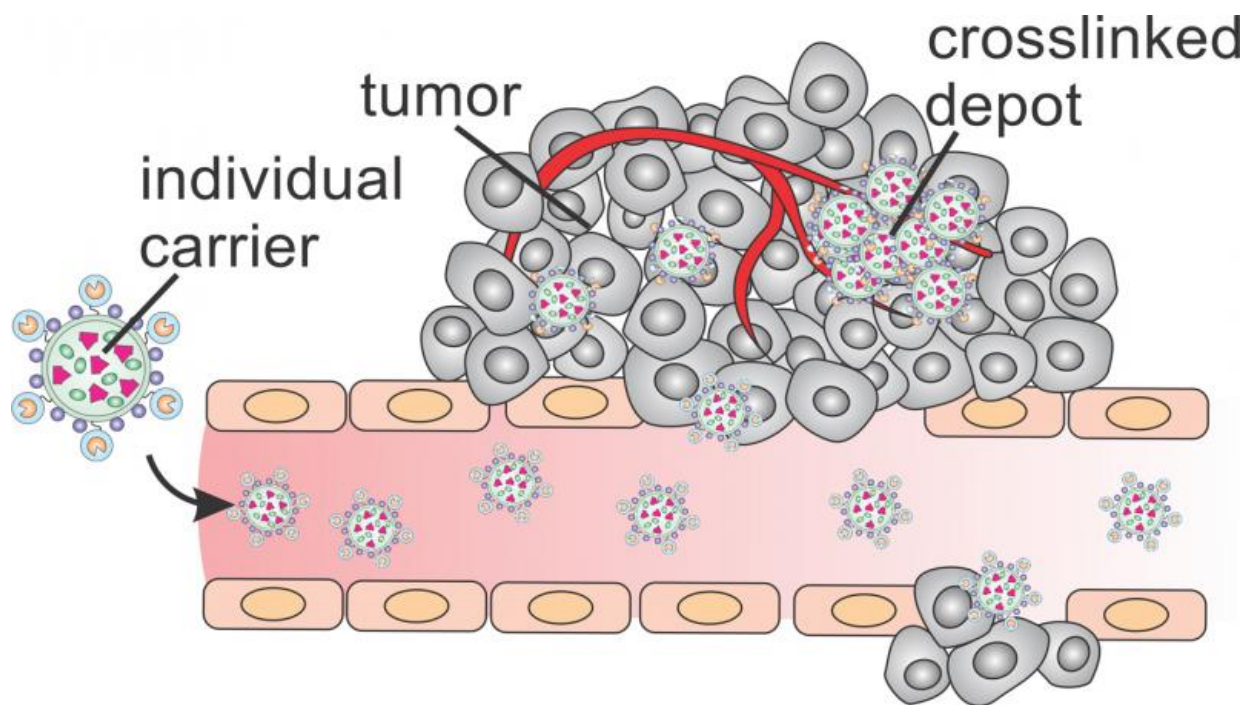


Microscopic drug 'depots' boost efficacy against tumors in animal model

January 25 2016, by Matt Shipman



Biomedical engineering researchers have developed a technique for creating microscopic "depots" for trapping drugs inside cancer tumors. In an animal model, these drug depots were 10 times more effective at shrinking tumors than the use of the same drugs without the depots. Credit: Quanyin Hu

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shrinking tumors than the use of the same drugs without the depots.

Some anti-cancer drugs are most effective outside of [cancer cells](#). For example, the anti-cancer drug TRAIL attacks a cancer cell's cell membrane, while another drug, cilengitide, inhibits the growth of blood vessels around a tumor, starving it of nutrients.

To improve the effectiveness of these drugs, scientists want to both prevent them from being absorbed into the cancer cells and prevent them from being washed away from the tumor site by the circulatory system.

"We have now found a way to do both, by creating micro-scale depots of these drugs inside a tumor," says Zhen Gu, corresponding author of a paper on the work and an assistant professor in the joint department of biomedical engineering at North Carolina State University and the University of North Carolina at Chapel Hill.

The researchers begin by creating a drug cocktail of TRAIL and cilengitide, then wrap the cocktail in a "nanocarrier" that is 100 nanometers (nm) in diameter. The nanocarrier is then studded with human serum albumin (HSA), an abundant protein in human blood.

The 100-nm nanocarrier is also studded with smaller nanocapsules - only 10 nm in diameter - that are made of a hyaluronic acid gel and contain an enzyme called transglutaminase (TG). The nanocarriers are then injected into the blood stream.

Some cancer tumors produce large quantities of an enzyme called hyaluronidase, which breaks up hyaluronic acid. So, when the nanocarriers enter a cancer tumor, the hyaluronidase dissolves the small hyaluronic acid gel nanocapsules on their surface. This releases the TG enzymes, which help to connect the HSA proteins studding the surface of other nanocarriers, creating a cross-linked [drug](#) depot inside the

tumor.

The size of the cross-linked depot largely prevents it from being absorbed by individual cancer cells or from being quickly swept away in the bloodstream. In addition, the TG can also help nanocarriers bind to other proteins in the tumor, helping to hold the depot in place.

The environment inside the tumor is also more acidic than its surroundings, and this acidity slowly breaks down the nanocarriers.

"This ensures a gradual, sustained release of the TRAIL and cilengitide into the tumor environment, maximizing the effectiveness of the drugs," Gu says.

The researchers evaluated this technique using breast [cancer tumors](#) in mice.

"We found that the use of cross-linked depots to deliver TRAIL and cilengitide shrunk tumors tenfold more than the use of the same dose of those drugs using conventional techniques," says Quanyin Hu, lead author of the paper and a Ph.D. student in the joint biomedical engineering department at NC State and UNC-Chapel Hill.

"This is a proof-of-concept study and additional work needs to be done to develop the technique," Gu says. "But it is promising, and we think this strategy could also be used for cancer immunotherapy. We would need to do more work in an animal model before pursuing clinical trials."

Gu also notes that it is too early to estimate costs associated with the technique.

"We're in the early stages of developing this technique, and we're trying

to make the process simpler and more effective - which would drive down manufacturing costs," Gu says. "That makes it difficult to estimate what the potential cost might be.

"And while we don't foresee any significant health risks beyond those posed by whatever drugs are being delivered, one reason we do animal and clinical trials is to identify any unforeseen risks."

The paper, "Tumor Microenvironment-Mediated Construction and Deconstruction of Extracellular Drug-Delivery Depots," was published Jan. 19 in the journal *NanoLetters*. The paper was co-authored by Wujin Sun, Yue Lu, Hunter Bomba, and Yanqi Ye in the joint [biomedical engineering](#) department at NC State and UNC-Chapel Hill; Tianyue Jiang of Nanjing Tech University; and Ari Isaacson of UNC-Chapel Hill. The work was supported by NC TraCS, NIH's Clinical and Translational Science Awards at UNC-CH, grant number 1UL1TR001111.

More information: Quanyin Hu et al. Tumor Microenvironment-Mediated Construction and Deconstruction of Extracellular Drug-Delivery Depots, *Nano Letters* (2016). [DOI: 10.1021/acs.nanolett.5b04343](#)

Provided by North Carolina State University

Citation: Microscopic drug 'depots' boost efficacy against tumors in animal model (2016, January 25) retrieved 24 June 2024 from <https://phys.org/news/2016-01-microscopic-drug-depots-boost-efficacy.html>

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