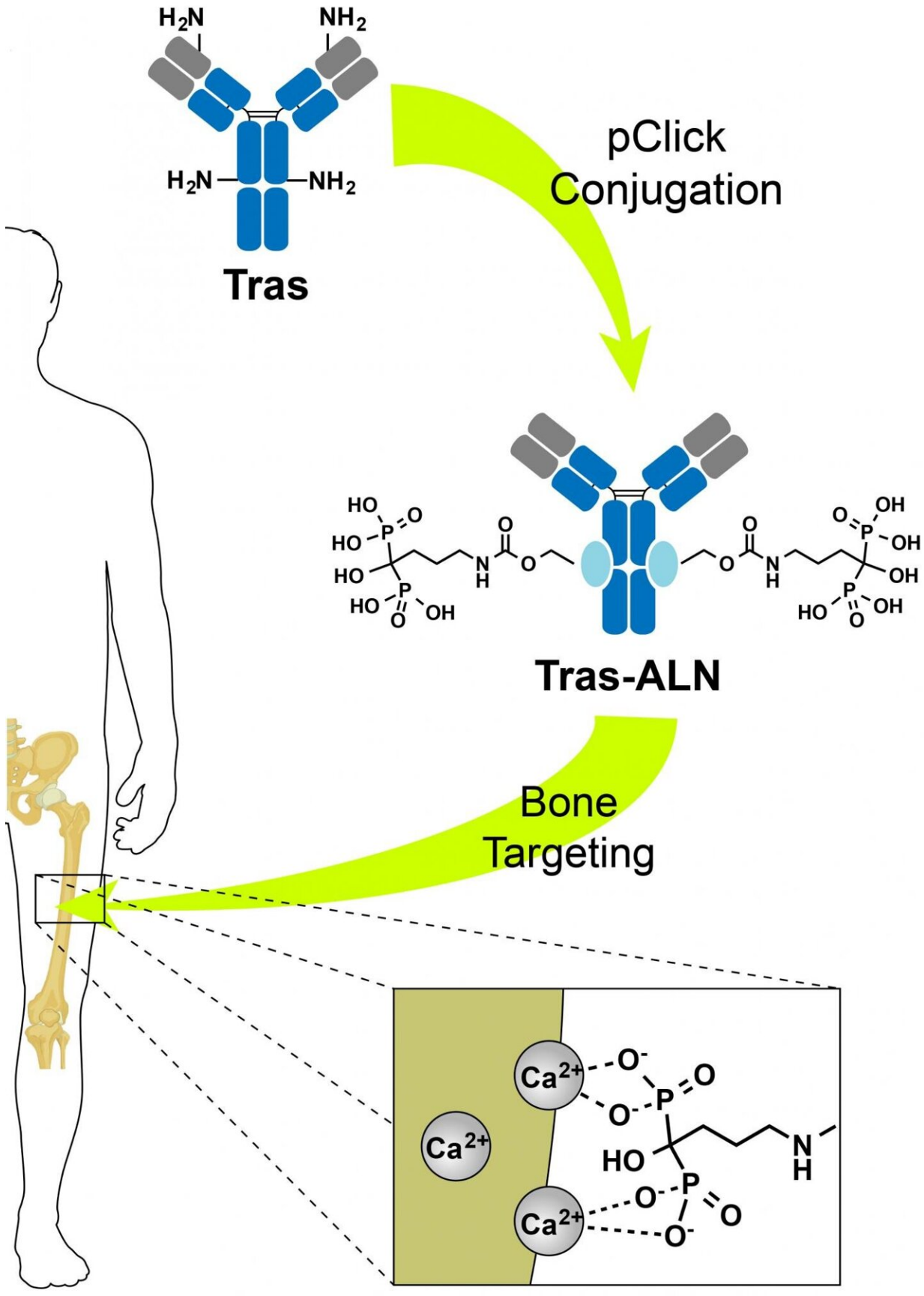
# Drug doubles down on bone cancer and metastasis

June 23 2021, by Mike Williams


H2N
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Scientists at Rice University and Baylor College of Medicine are using pClick conjugation to create therapeutic antibodies that target bone cancers. The conjugate incorporates bisphosphonate molecules that bind to the bone hydroxyapatite matrix. Credit: Baylor College of Medicine/Rice University

Bone cancer is hard to treat and prone to metastasis. Research teams at Rice University and Baylor College of Medicine have a new strategy to attack it.

Chemist Han Xiao at Rice and biologist Xiang Zhang at Baylor and their labs have developed an antibody conjugate called BonTarg that delivers drugs to bone tumors and inhibits metastasis.

Their open-access study, which appears in *Science Advances,* shows how Xiao's pClick technology can be used to link bone-targeting antibodies and therapeutic molecules.

In experiments, they used pClick to couple a molecule used to treat osteoporosis, alendronate, with the HER2-targeting antibody trastuzumab used to treat breast cancer, and found it significantly enhanced the concentration of the antibody at tumor sites.

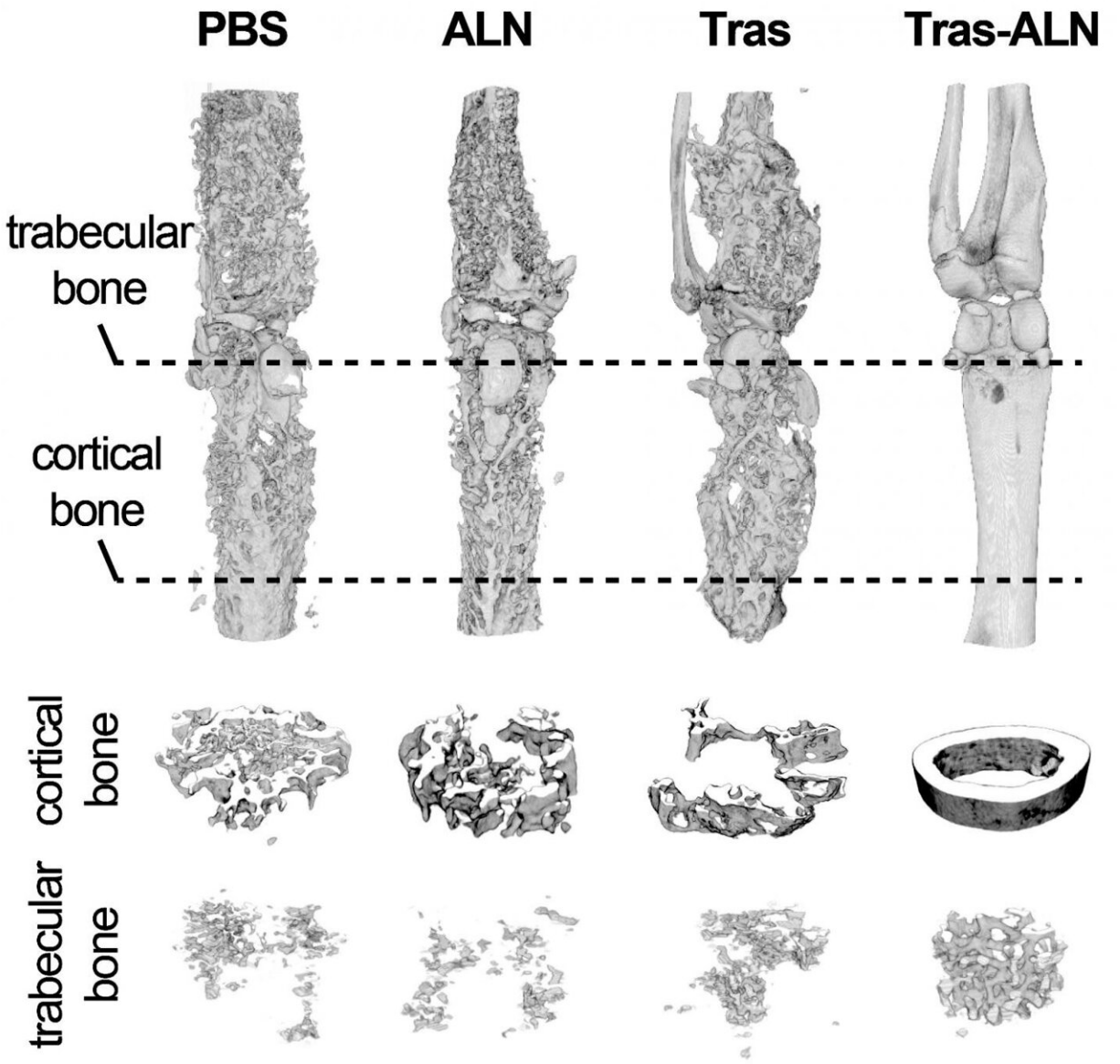
They reported the combination also inhibited secondary metastasis from infected organs seeded by bone tumors.

"Bone cancer is really challenging to treat, and clinical trials of different treatments have been disappointing for people with bone metastasis," said Xiao, who joined Rice in 2017 with funding from the Cancer Prevention and Research Institute of Texas (CPRIT). "We feel our

strategy is a real game changer."

"Getting effective concentrations of drugs to bone tumors has been challenging because bones are hard, their network of blood vessels is limited and drugs have tended to attach to adjacent healthy tissues," Zhang said.

The new strategy employs bisphosphonates, a class of drugs typically used to treat osteoporosis. Bisphosphonates have a high binding affinity for hydroxyapatite, the main component of hard bone, and help overcome physical and biological barriers in the bone microenvironment.




MicroCT scans of rodents show those treated with the conjugate of trastuzumab and alendronate (far right), created at Rice University and Baylor College of Medicine, fared far better than those treated with phosphate-buffered saline (PBS) or alendronate (ALN) or trastuzumab (Tras) alone 82 days after tumor implantation. Credit: Baylor College of Medicine/Rice University

They're also amenable to binding with drugs through pClick, which uses a cross-linker to snap to specific sites on antibodies without having to re-engineer them with harmful chemicals, enzymes or ultraviolet light.

The result is a molecule that seeks out bone tumors and stays put, giving the drug time to kill tumor cells. It helps that bisphosphonate molecules prefer acidic sites like bone tumors, keeping the drug concentration higher there than in surrounding healthy tissue.

The researchers chose breast cancer drugs because while many recover from the disease, 20 to 40% of breast cancer survivors eventually suffer metastases to distant organs, with metastasis to bone occurring in about 70% of these cases, significantly increasing mortality, they said.

While chemotherapy, hormone and radiation therapy used to treat women with bone metastatic breast cancers can shrink or slow bone metastasis, they usually do not eliminate the metastases, Xiao said.

"Bone is kind of a fertile soil for cancer cell," Xiao said. "If a cancer cell reaches it, then it has a really good chance to grow and to further migrate, for example to the brain, the heart, the liver or to other tissues. That's a really bad situation for a patient."

Xiao hopes to get the compound into a clinical trial, and sees potential for custom conjugates that treat other tumors prone to metastasis, including prostate cancer.

Postdoctoral researchers Zeru Tian of Rice and Ling Wu of Baylor are co-lead authors of the paper. Co-authors are graduate students Chenfei Yu, Yuda Chen, Axel Loredo and Kuan-Lin Wu and postdoctoral researcher Lushun Wang of Rice; and postdoctoral fellows Zhan Xu, Igor Bado and Weijie Zhang and instructor Hai Wang of Baylor.

Xiao is the Norman Hackerman-Welch Young Investigator, the Cancer Prevention and Research Institute of Texas (CPRIT) Scholar in Cancer Research and an assistant professor of chemistry, bioengineering and biosciences. Zhang is the William T. Butler, M.D., Endowed Chair for Distinguished Faculty, McNair Scholar, associate director of the Lester and Sue Smith Breast Center, professor of molecular and cellular biology and member of the Dan L Duncan Comprehensive Cancer Center.

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**More information:** "Harnessing the power of antibodies to fight bone metastasis" *Science Advances* (2021). DOI: 10.1126/sciadv.abf2051 , advances.sciencemag.org/content/7/26/eabf2051

Provided by Rice University