Improved chemokine homing enhances CAR T–cell therapy for osteosarcoma

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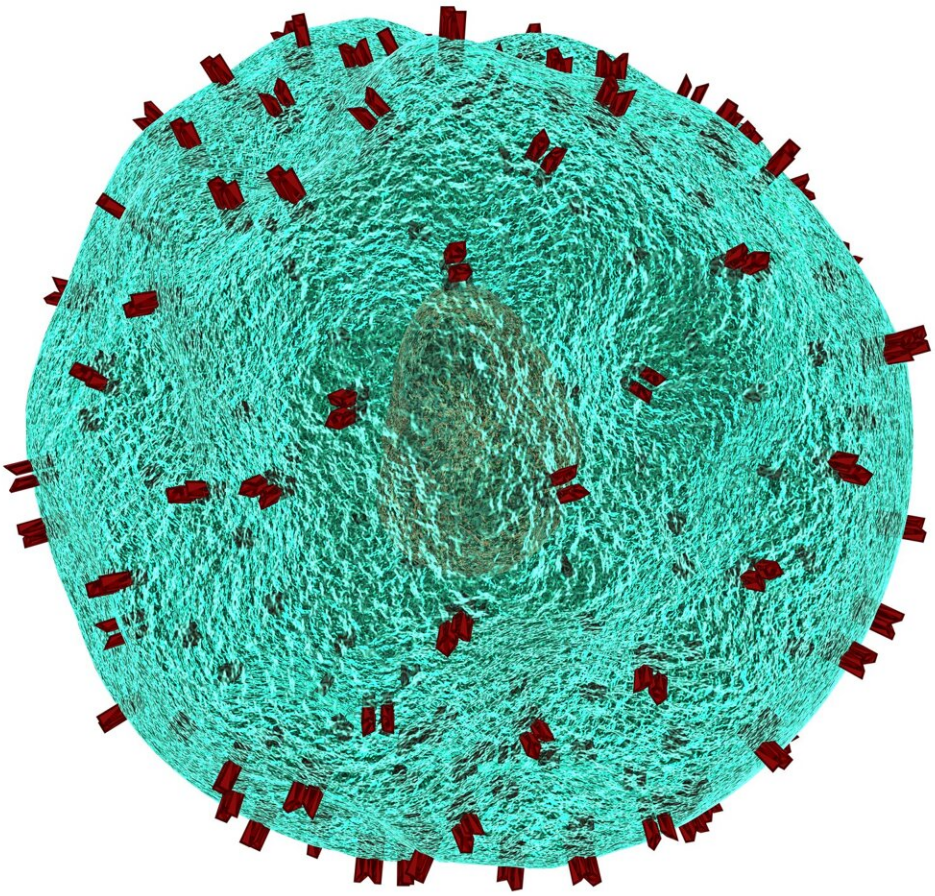

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Chimeric antigen receptor (CAR) T–cell immunotherapy re-engineers a patient's immune cells to target cancer cells. While successful in some types of leukemia, the approach has yet to realize its potential against pediatric solid tumors.

Scientists at St. Jude Children's Research Hospital have identified a way to improve CAR T–cell homing—a T cell's ability to navigate effectively to a tumor—for osteosarcoma. Improved homing is a necessary step in designing more successful CAR T–cell therapies. The results were published today in *Clinical Cancer Research*.

Osteosarcoma is the most common type of bone cancer in children and teens. It typically starts in the wide ends of long bones, such as the legs, but can also occur in other bones, such as the pelvis and skull. Approximately 15–20% of patients with osteosarcoma already have metastatic disease when they are diagnosed, and less than 20% of those with metastatic or relapsed disease survive beyond three years.

Treatment for osteosarcoma includes surgery and chemotherapy—approaches that have been a mainstay of care for over 50 years. This underscores the need for novel, more modern therapeutic approaches such as immunotherapy. However, solid tumors present additional challenges that any CAR T–cell technology must overcome to succeed.

"Solid tumors are just that, solid—these are hard, dense masses which are difficult for immune cells to penetrate," said first and corresponding author Lindsay Talbot, MD, St. Jude Department of Surgery. "For immunotherapy to work for solid tumors we need to attract T cells to the

tumor, help them penetrate it and keep them there to generate a prolonged response."

Talbot and her colleagues focused on the first step: homing.

Unique chemokines help T cells home to cancer

Imagine a dog that wants to find their favorite bone, lost somewhere in the backyard—they would use their nose to track the scent of the bone to its location. A T cell is like a dog, the bone is like a tumor and the scent the bone emits is like a chemokine.

Chemokines are proteins secreted by cells in the body, such as tumor cells, to attract immune cells. Homing happens when the bone's scent reaches the dog—it will zero in on the bone's location and go there. However, T cells' "noses" often cannot pick up the scent of cancer cells, i.e., T cells do not express the receptors, which recognize the chemokines secreted by tumors. T-cell engineering can overcome this chemokine/chemokine receptor mismatch.

There are approximately 50 chemokines and 20 chemokine receptors in humans. To improve CAR T–cell homing to osteosarcoma, the researchers had to first determine which chemokines are expressed by that particular cancer type.

"We used patient specimens gathered after surgery to guide us to which chemokines to target in osteosarcoma, agnostically screening for the ones produced by the tumor—that's as close to what occurs inside a patient as we can get," explained Talbot, an active surgeon at St. Jude. "When you combine that with gene expression data, you get very robust results about which chemokines are important for a specific type of cancer."

Using this approach, the researchers identified two chemokines, CXCL8 and CXCL16, secreted by osteosarcoma. However, CAR T cells do not express the receptors for these chemokines.

A first step toward realizing immunotherapy for osteosarcoma

Having identified this chemokine/chemokine receptor mismatch, the researchers modified CAR T cells targeting the osteosarcoma antigen B7-H3 to express the receptors (CXCR2 or CXCR6) for the identified chemokines. They evaluated the homing kinetics (movement) and efficiency of the modified cells—testing their ability to find and infiltrate osteosarcoma.

The researchers found that the engineered cells behaved differently. Those expressing CXCR2 quickly homed and arrived at the tumor but plateaued in their activity early. Those expressing CXCR6 took a little longer to home, but similarly plateaued. Notably, the researchers observed prolonged survival in a model of metastatic disease using the CXCR2 or CXCR6 modified B7-H3-CAR T cells compared to unmodified B7-H3-CAR T cells.

"We haven't changed anything about how the T cells kill the tumor cells; what we've changed is how well they get to the tumor, and that has implications for specificity and toxicity," said Talbot. "But the work isn't over, and I'm very excited about the opportunity to continue making strides toward solid tumor immunotherapy with this platform."

Looking ahead, paper author Christopher DeRenzo, MD, MBA, St. Jude Department of Bone Marrow Transplantation & Cellular Therapy, reflects on the findings' clinical implications. "Immunotherapy has tremendous potential as a treatment for cancer, but there is still a lot of

work to be done to realize that potential in pediatric solid tumors. Improving CAR T cells to better home to osteosarcoma is an exciting advance, so we are working on connecting laboratory discoveries like this with what we can do for patients through clinical trials," he said.

Stephen Gottschalk, MD, St. Jude Department of Bone Marrow Transplantation & Cellular Therapy chair and an author on the paper, sums up the works' implications, "By devising a strategy to increase the homing of CAR T cells to osteosarcoma sites, Dr. Talbot and her team were able to demonstrate that these cells have improved anti-tumor activity in preclinical models."

He adds, "Based on these findings, we are committed to translating these 'improved osteosarcoma finder' CAR T cells into early phase clinical testing."

More information: Lindsay J. Talbot et al, Redirecting B7-H3.CAR T cells to Chemokines Expressed in Osteosarcoma Enhances Homing and Antitumor Activity in Preclinical Models, *Clinical Cancer Research* (2024). DOI: 10.1158/1078-0432.CCR-23-3298

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