Researchers at University of California San Diego have found that the most common form of liver cancer—one with a high mortality rate—can be better targeted and treated using an innovative new stem cell-derived
therapy, according to a recently published study in *Cell Stem Cell*.

The treatment, not yet studied in patients, involves the lab engineering of natural killer (NK) cells—white blood cells that destroy tumor cells—to more effectively battle hepatocellular carcinoma (HCC), one of the most treatment-resistant types of solid tumor.

Genetically modified NK-cell therapy doesn't require personalization like chimeric antigen receptor (CAR)-expressing T-cell therapy—a relatively new, personalized form of immunotherapy. That means an NK-cell therapy could be mass-produced and shelf-ready for patients, who could begin therapy without delay, their new research shows.

"To some extent all tumor cells—perhaps hepatocellular carcinoma more so—inhibit immune cells that try to kill them," said UC San Diego School of Medicine Professor Dan Kaufman, M.D., Ph.D., lead author on the study, director of the Sanford Advanced Therapy Center at the university's Sanford Stem Cell Institute and Moores Cancer Center member.

"This is one key reason why some immunotherapies like CAR T cells have been less successful for solid tumors than for blood cancers—the immunosuppressive tumor microenvironment."

Kaufman and his team produced stem cell-derived NK cells in which the receptor for transforming growth factor beta (TGF-β)—a protein that impairs immune function—was disabled. HCC tumors and the liver in general contain copious amounts of the substance, which both inhibits immune cell activity and allows cancer to proliferate.

They found that typical NK cells without the disabled receptor, like CAR T cells, were not very effective in battling the cancer. "These are pretty resistant tumors—when we put them in mice, they grow and kill
the mice," he said. The five-year survival rate for HCC in humans is less than 20%.

When researchers tested the modified NK cells against the cancer, however, "we got very good anti-tumor activity and significantly prolonged survival," he noted.

"These studies demonstrate that it is crucial to block transforming growth factor beta—at least for NK cells, but I also think it's true for CAR T cells," Kaufman said. "If you unleash NK cells by blocking this inhibitory pathway, they should kill cancer quite nicely."

Kaufman anticipates that his team's discovery will manifest itself in the clinical trials of many research groups and companies—whether they're working on CAR T-cell or NK-cell therapies, battling hepatocellular carcinoma or other challenging types of solid tumors.

"Anyone developing such therapies for solid tumors should be working to inhibit transforming growth factor beta activity to improve cancer-killing and attain effective anti-tumor activity," he said.

Co-authors of this study include Jaya Lakshmi Thangaraj; Michael Coffey; and Edith Lopez, all of the Division of Regenerative Medicine at UC San Diego's School of Medicine.

**More information:** Jaya Lakshmi Thangaraj et al, Disruption of TGF-β signaling pathway is required to mediate effective killing of hepatocellular carcinoma by human iPSC-derived NK cells, *Cell Stem Cell* (2024). DOI: 10.1016/j.stem.2024.06.009. www.cell.com/cell-stem-cell/f...1934-5909(24)00217-0