Research reveals an immune cell that can attack cancer

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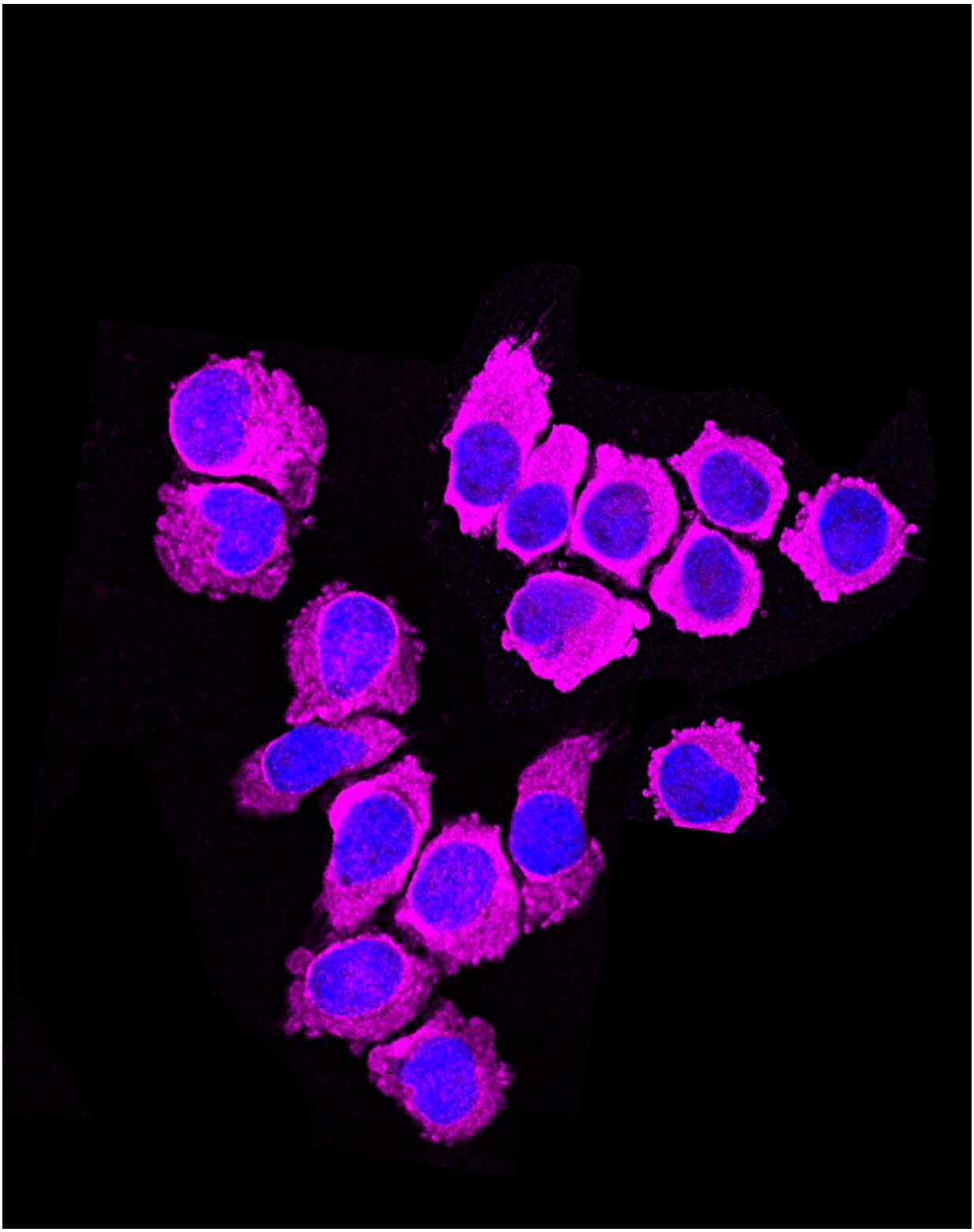

City of Hope researchers discovered that ILC2s can attack cancer cells. Credit: City of Hope

According to preclinical research published in *Cell* researchers at City of Hope have discovered that a type of immune cell in the human body known to be important for allergy and other immune responses can also attack cancer.

Furthermore, these cells, called human type 2 innate lymphoid cells (ILC2s), can be expanded outside of the body and applied in larger numbers to overpower a tumor's defenses and eliminate malignant cells in mouse models with cancer.

"The City of Hope team has identified human ILC2 cells as a new member of the cell family capable of directly killing all types of cancers, including blood cancers and solid tumors," said Jianhua Yu, Ph.D., a professor in the Department of Hematology & Hematopoietic Cell Transplantation at City of Hope and the study's senior author.

"In the future, these cells could be manufactured, preserved by freezing, and then administered to patients. Unlike T cell-based therapies like CAR T cells, which necessitate using the patient's own cells due to their specific characteristics, ILC2s might be sourced from healthy donors, presenting a distinct potential therapeutic approach as an allogeneic and 'off-the-shelf' product."

In previous research focused on mouse cells, ILC2s had not consistently shown promise when tested for their cancer-killing abilities.

However, in the highly translational labs at City of Hope, researchers prioritized the examination of human cells and found that human ILC2s do not work the same as mouse ILC2s.

"Typically, mice are reliable models for predicting human immunity, so

it was a real surprise in the field to find that human ILC2s function as direct cancer killers while their mouse counterparts do not," said Michael Caligiuri, M.D., who is a co-senior author of the study and also a City of Hope professor in the Department of Hematology & Hematopoietic Cell Transplantation. "It is remarkable that something has evolved so distinctly in going from mouse to human."

Finding a new function

To test human ILC2s, Yu and the team first isolated the cells from a blood sample. Then, they developed a novel platform that in four weeks can expand ILC2s harvested from the body 2,000-fold.

They next injected these externally expanded ILC2s into mice engrafted with human acute myeloid leukemia (AML) or solid tumors, including pancreatic cancer, lung cancer and glioblastoma. The results showed that this ILC2 population could kill these tumors via a previously unknown cancer-killing mechanism.

"One convincing and direct piece of evidence appeared when we placed one ILC2 and one tumor cell directly together and found that the tumor cell died, but the ILC2 cell survived," explained Yu. "This proves that the ILC2s directly killed the cancer cell in that absence of any other cell."

Yu noted that the ILC2s do not need to come from the cancer patient's own cells, meaning that there may be the possibility of harvesting and freezing ILC2s from healthy donors for ILC2 treatment options in the future.

Investigating killer cells

Yu and Caligiuri have been investigating a different type of cancer killer

called natural killer cells, or NK cells, for decades. In fact, Yu is founding director of the Natural Killer Cell Biology Research Program at City of Hope, a national leader in the field.

Yu and Caligiuri said ILC2s now represent a new member of the cytotoxic immune effector cell family, alongside NK cells and $CD8^+$ T cells, which help the body fight against cancer. They are excited to see how researchers might be able to harness the collective power of these different killer cells to better fight other diseases as well.

Yu and Caligiuri caution that because they are still in the early days of understanding ILC2s' cancer-killing functions, many questions remain. However, they plan to continue to work with their collaborators to understand and learn more about human ILC2s now that they know the cells are assassins.

"We aim to really expand the applications of these findings, potentially beyond cancer treatments," Yu said, noting that ILC2s may even work against viruses, such as COVID-19. "Additionally, we are working toward translating our discovery into tangible clinical benefits."

The team has already jumped at least one hurdle in getting ILC2s to clinical trials, which is having enough of the product to test. ILC2s are rare in the body, Caligiuri said, found in highest numbers in the lungs, gut and skin. The team has a platform to grow them quickly.

"You have to be able to expand these cells for human clinical trials and one of the exciting things is that we are on the right track," Caligiuri said. "At City of Hope, we have the advantage of access to our good manufacturing practices-compliant facilities that can manufacture cells for us and speed discoveries into clinical trials."

The study team also included lead authors Zhenlong Li, Rui Ma and

Hejun Tang from the Yu and Caligiuri labs, as well as David Artis, Ph.D., the Michael Kors Professor of Immunology and director of the Jill Roberts Institute for Inflammatory Bowel Disease Research at Weill Cornell Medicine.

More information: Zhenlong Li et al, Therapeutic application of human type 2 innate lymphoid cells via induction of granzyme B-mediated tumor cell death, *Cell* (2024). DOI: 10.1016/j.cell.2023.12.015

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