Medical Xpress

3D-printed mini-tumors mimic human tissue for cancer immunotherapy tests

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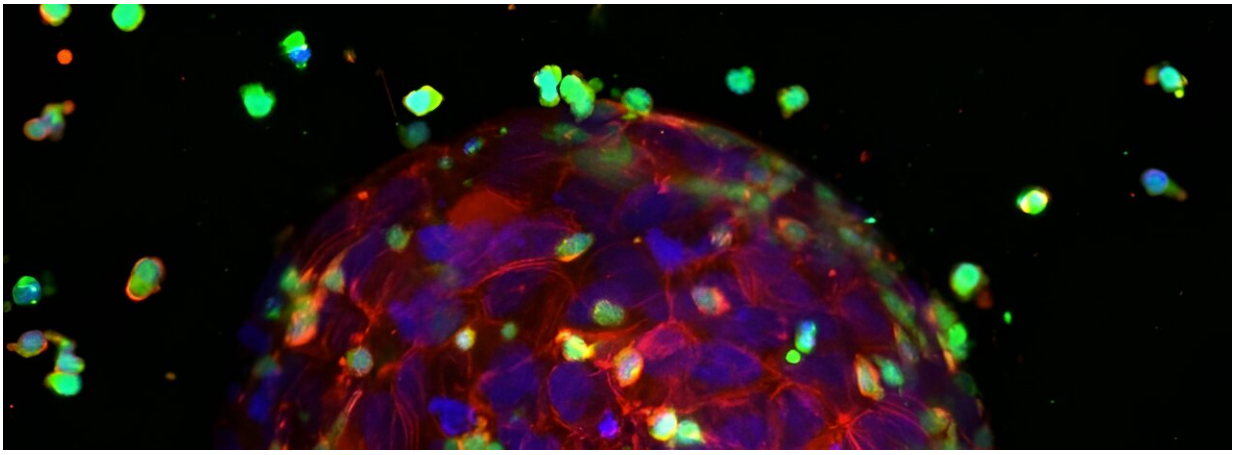


A tumour attacked by T-cells in the assay. Blue and Red: nuclei and cytoskeleton of the tumour cells. Green: T-cells. Credit: Chen-Yi Liao et al, CD3-engaging bispecific antibodies trigger a paracrine regulated wave of T-cell recruitment for effective tumor killing, *Communications Biology* (2024). DOI: 10.1038/s42003-024-06682-9

Leiden researchers have developed a model to advance cancer immunotherapy. Using a 3D printer, they create mini-tumors within an environment that closely mimics human tissue. They have also developed a method to monitor real-time interactions of these mini-tumors with immune cells during tests.

Researchers at the Leiden Academic Center for Drug Research have

introduced a new approach to assess the efficacy of cancer immunotherapies. "We use this method to test enhanced T-cells and bispecific antibodies for their effectiveness," explains Ph.D. candidate Anita Liao. "This ensures that only the most promising candidates move forward for further research and clinical development."

Immunotherapy: Helping immune cells attack tumors

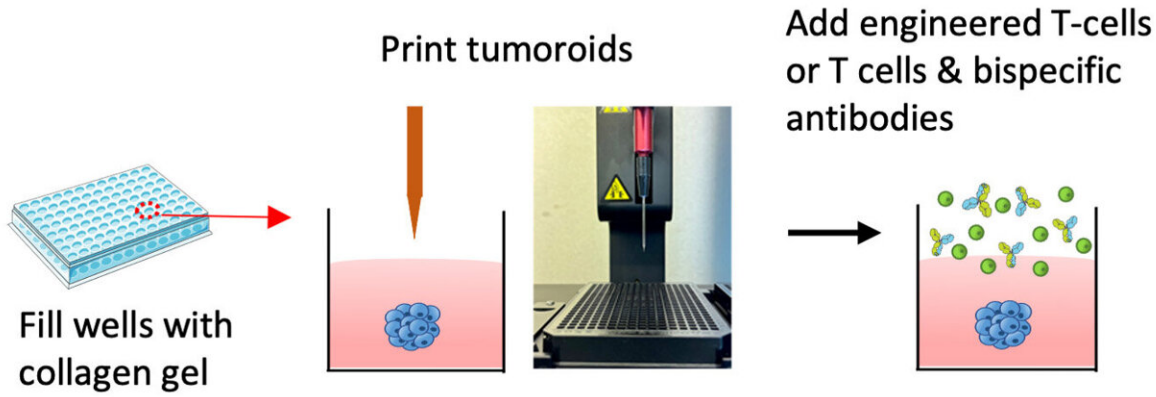
Cancer cells are adept at evading detection. They use various strategies to hide from the immune system and even repel attacks. Immunotherapy aids the immune system in recognizing, attacking, and ultimately destroying cancer cells. This can be achieved by strengthening the immune system with drugs, making cancer cells more detectable, or by artificially enhancing T-cells. The Leiden research focuses on innovative testing strategies for the latter two approaches.

- Adaptive T-cell therapy: T-cells are specialized immune cells that can attack cancer cells. They have receptors on their surface that act like antennas to identify cancer cells. By isolating a patient's T-cells, engineering them with better antennas, and transfusing them back into the blood, T-cells can be engineered to better recognize and attack cancer cells.
- Bispecific antibodies: These antibodies bind to T-cells with one arm and to cancer cells with the other. This way, they help T-cells locate and destroy cancer cells more effectively.

From petri dishes to realistic models

Traditionally, new immunotherapies are tested by culturing tumor cells, T-cells, and sometimes antibodies together in a petri dish and observing their interactions. However, this method does not accurately reflect the complexity of the human body.

"In a petri dish, T-cells grow among tumor cells and can immediately start killing them," explains Erik Danen, Professor of Cancer Drug Target Discovery. "In reality, T-cells must navigate to the tumor first, which adds complexity."



A 3D bioprinter creates small, three-dimensional tumors in a collagen gel that continue to grow. The researchers then add T-cells and observe what happens. Credit: Chen-Yi Liao et al, CD3-engaging bispecific antibodies trigger a paracrine regulated wave of T-cell recruitment for effective tumor killing, *Communications Biology* (2024). DOI: 10.1038/s42003-024-06682-9

3D-printed mini-tumors and real-time monitoring

The researchers have developed a more realistic model using 3D-printed mini-tumors embedded in a collagen gel. Liao said, "This gel mimics human tissue. We use a 3D bioprinter with a special needle to inject tumor cells into the gel, creating small, three-dimensional tumors.

"They grow and invade into the gel and closely resemble real tumors in the body. Next, T-cells are added that have to find their way to the tumor. The method is high-throughput and suitable for testing enhanced T-cells and antibodies."

Additionally, the team has created a system to monitor these mini-tumors in real-time using automated microscopes. This allows them to observe what happens inside and around the tumor and follow the immune cells. Danen added, "We can see not only if and how enhanced T-cells and antibodies work but also investigate the defensive strategies employed by tumor cells."

Insight into effectiveness: A new testing method makes a difference

The new method has already proven successful in testing various bispecific antibodies. The researchers found that not all antibodies were effective, contrary to what older models suggested. The research is published in the journal *Communications Biology*.

Danen says, "In the new, more complex model, we observed that the most effective antibodies not only activate T-cells but also trigger the production of signaling molecules that attract additional T-cells. With the old method, the antibodies did not have a chance to reveal this behavior, because T-cells were mixed with tumor cells and could begin killing them immediately. Our new method will help identify the most effective antibodies for further clinical development."

The team already uses their model to test improved T-cell receptors. For instance, they are evaluating receptors developed by immunologist Mirjam Heemskerk from Leiden University Medical Center for eye cancer treatment. They have also collaborated with Reno Debets'

immunology lab at Erasmus Medical Center in Rotterdam to test new receptors for breast cancer therapy. The paper is published in the journal *Cancer Discovery*.

"Our model has successfully predicted which receptors will be effective in mouse models," Danen concludes.

"These enhanced receptors are now ready for clinical trials in real patients. We hope our research represents a significant step forward in selecting optimal treatment for cancer patients."

More information: Chen-Yi Liao et al, CD3-engaging bispecific antibodies trigger a paracrine regulated wave of T-cell recruitment for effective tumor killing, *Communications Biology* (2024). DOI: 10.1038/s42003-024-06682-9

Dian Kortleve et al, TCR-engineered T-cells directed against Ropporin-1 constitute a safe and effective treatment for triple-negative breast cancer, *Cancer Discovery* (2024). DOI: 10.1158/2159-8290.CD-24-0168

Provided by Leiden University