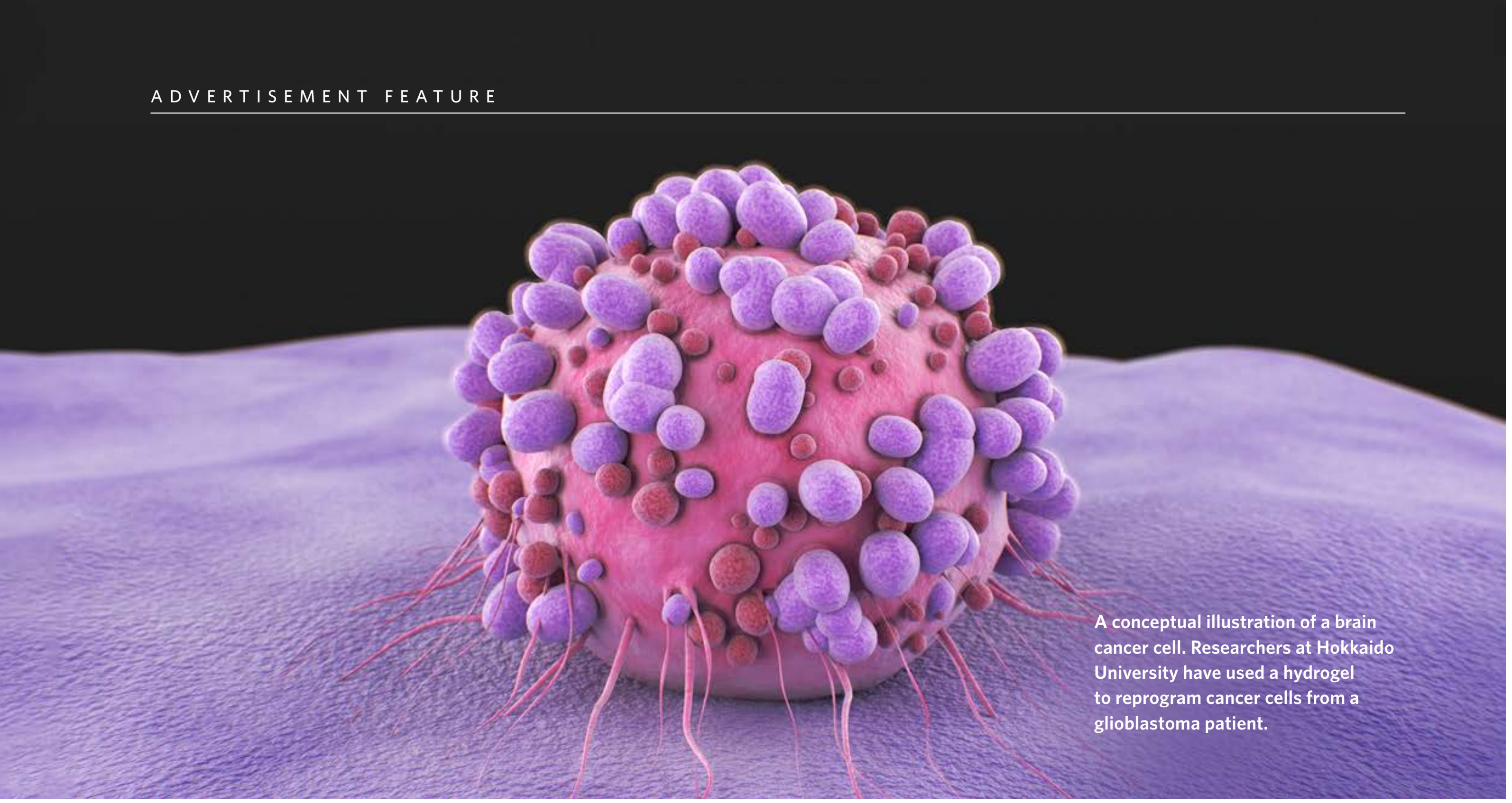


A conceptual illustration of a brain cancer cell. Researchers at Hokkaido University have used a hydrogel to reprogram cancer cells from a glioblastoma patient.

HYDROGEL-BASED MATERIALS: A NEW WEAPON AGAINST CANCER?

Reprogramming cancer cells into cancer stem cells using synthetic polymer hydrogels could OPEN EXCITING OPPORTUNITIES FOR DRUG DEVELOPMENT AND PERSONALIZED MEDICINE.

While advances in cancer prevention, diagnosis and treatment have improved survival rates, the disease remains a leading cause of death globally. In 2022, there were nearly 20 million new cases and 9.7 million cancer-related deaths worldwide.

A critical research challenge in improving long-term survival rates is eliminating cancer stem cells (CSCs). These rare and elusive cells — accounting for as few as one in a million cancer cells in a tumour — have exceptional abilities to self-renew and sustain tumour growth[1]. They are highly resistant to conventional treatments such as chemotherapy and radiotherapy. And they can hide or circulate in the body, causing cancer to recur or spread.

"CSCs are a major target for anti-cancer drugs, but they are difficult to identify because they are present in very small numbers in cancer tissues," says Shinya Tanaka, a professor at the Department of Cancer Pathology at Hokkaido University, Japan. "Understanding the molecular mechanisms of CSCs is crucial for developing better cancer treatments."

To solve this problem, an interdisciplinary collaboration between materials scientists, biologists and clinicians in the Institute for Chemical Reaction Design and Discovery (ICReDD) and Hokkaido University Hospital has been searching for innovative solutions. The researchers have discovered that fully differentiated cancer cells can be rapidly reprogrammed into CSCs by using a double-network hydrogel — a soft but tough material composed of two interpenetrating chemical networks[2].

This new method allows cancer researchers to generate a potentially unlimited supply of CSCs for research, thereby accelerating efforts to identify effective new therapies to combat treatment resistance and prevent relapse.

HARP REPROGRAMMING

Consisting mostly of water, synthetic polymer hydrogels are soft materials that closely resemble biological tissues, making them highly suitable for biomedical applications. Among them, double-network hydrogels have emerged as particularly promising biomaterials due to their combination of toughness and softness[2].

The team at Hokkaido University hypothesized that a specific double-network hydrogel — consisting of 2-acrylamido-2-methyl-1-propanesulfonic acid and N,N'-dimethylacrylamide — could provide the right conditions to induce the development of CSCs[1,2].

"To our surprise, cancer cells formed spheres containing CSCs within 24 hours when they were placed on our double-network hydrogel," describes Tanaka. "We call this phenomenon hydrogel-activated reprogramming phenomenon, or HARP for short."

In the laboratory the researchers successfully reprogrammed six human cancer cell lines — brain, womb, lung, bowel, bladder and sarcoma — into CSCs using the double-network hydrogel. Crucially, they demonstrated that brain tumour cells from a glioblastoma patient could also undergo rapid and robust reprogramming. When these cancer cells were transplanted into the mouse brain, they efficiently formed tumours, confirming their stemness properties[1].

luismmolina/iStock/Getty

While previous studies had used hydrogels for CSC research, they were restricted to maintaining stemness properties of CSCs or supporting the growth of CSCs. This discovery represents a significant step forward, say the researchers, as it demonstrates for the first time that hydrogels can revert fully differentiated cancer cells into CSCs. This promises to open up new avenues for understanding tumour biology and developing targeted therapies, says Tanaka.

BIOLOGICAL INSIGHTS

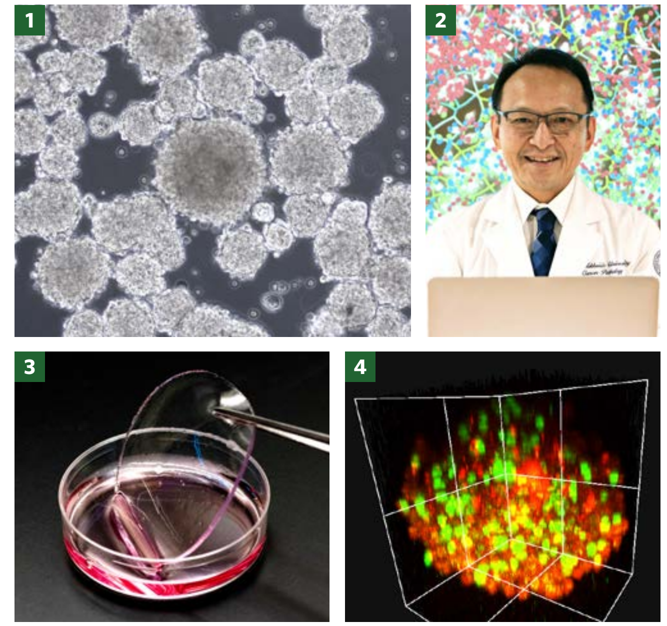
The researchers also uncovered some of the molecular mechanisms involved in the reprogramming of cancer cells into CSCs, offering potentially valuable insights into tumour biology and treatment resistance[3].

"We found that calcium channel receptors and the protein osteopontin were essential for inducing stemness in brain cancer cells," says Tanaka.

CSCs require very specific microenvironments, or 'niches' to thrive, with individual niches contributing to different aspects of tumour progression, spread and recurrence[3].

"Besides the double-network gel, we have identified several single-network hydrogels that can generate CSCs without forming spheroid structures," says Tanaka. "This raises the possibility that different hydrogels may mimic different CSC niches within heterogeneous cancer tissues, potentially offering insights into the diverse microenvironments that sustain CSCs."

The team has also uncovered how the physical and chemical properties of hydrogels might influence their ability to induce stemness in cancer cells[1,4].



▲ 1. Spheroids of brain cancer stem cells on a hydrogel.
2. Hokkaido University's Shinya Tanaka in his laboratory.
3. A double-network hydrogel being used to generate cancer stem cells.
4. Immunofluorescence analysis of SOX2 in spheroids.

"In HARP, we found that integrin or TRP family ion channels may function as mechanoreceptors receiving hydrogel stimulation," explains Tanaka. "This interaction activates various signalling pathways. And hydrogel siffness is also critical. Proteins such as growth factors and extracellular matrix secreted by cancer cells could be entrapped in the hydrogels, effectively acting as reservoirs to further support stemness."

CLINICAL APPLICATION

Beyond deepening the understanding of the biology of CSCs, the HARP phenomenon presents exciting new opportunities for advancing cancer diagnosis and treatment, argue the researchers.

A long-standing challenge to identifying or targeting CSCs in individual patients has been the lack of definitive biomarkers that distinguish these cells from other cancer cells.

"HARP has the potential to reveal new biomarkers for CSCs and the molecules essential for their survival," states Tanaka.

Recently, HARP led to the discovery in the lab of an essential component of human leukaemia stem cells, pinpointing AKR1B1 and TSPYL as potential targets for therapeutic development[5].

Exploiting HARP could also provide a tool for personalized medicine, providing key insights into CSCs that exist in a person's tumour to inform clinical decision making, say the researchers.

"By culturing cancer biopsies on hydrogels, CSCs can be rapidly generated and characterized," explains Tanaka. "This approach could one day enable doctors to select the most effective drugs to eradicate CSCs in individual patients, reducing the risk of recurrence."

Another tantalizing prospect is the potential application of HARP to drug screening. By enabling researchers to rapidly generate large quantities of CSCs, this could significantly accelerate the discovery and development of novel drug candidates aimed at targeting and eradicating these highly resistant cells.

FUTURE DIRECTIONS

With its potential to address critical gaps in understanding CSCs and their role in disease recurrence, the HARP phenomenon could drive significant advances in cancer diagnosis, treatment and personalized medicine, argue the researchers.

"With this fusion between materials science and medical research, we hope to dramatically increase the prognosis for cancer patients," says Tanaka.

While the current focus is on generating CSCs, the potential biomedical applications of using hydrogel-based cell reprogramming could extend beyond cancer.

"We're also exploring ways to use this system for regenerative medicine," says Tanaka. "My goal is to establish a new academic field dedicated to biomedical innovation using hydrogels as material genomics." ■

REFERENCES

1. Suzuka, J. *et al. Nat. Biomed. Eng.* **5,** 914–925 (2021).
2. Gong, J. P. *Science* **344,** 161–162 (2014).
3. Chu, X. *et al. Sig. Transduct. Targ. Ther.* **9,** 170 (2024).
4. Sun, Y. *et al. Biochem. Biophys. Res. Comm.* **743,** 151163 (2025).
5. Sawai, S. *et al. Biochem. Biophys. Res. Comm.* **744,** 151149 (2025).

HOKKAIDO UNIVERSITY

HOKKAIDO UNIVERSITY HOSPITAL

http://patho2.med.hokudai.ac.jp

Advertiser retains sole responsibility for content