Newton

GRAPHIC SCIENCE MAGAZINE Newton

The forefront of cancer immunotherapy

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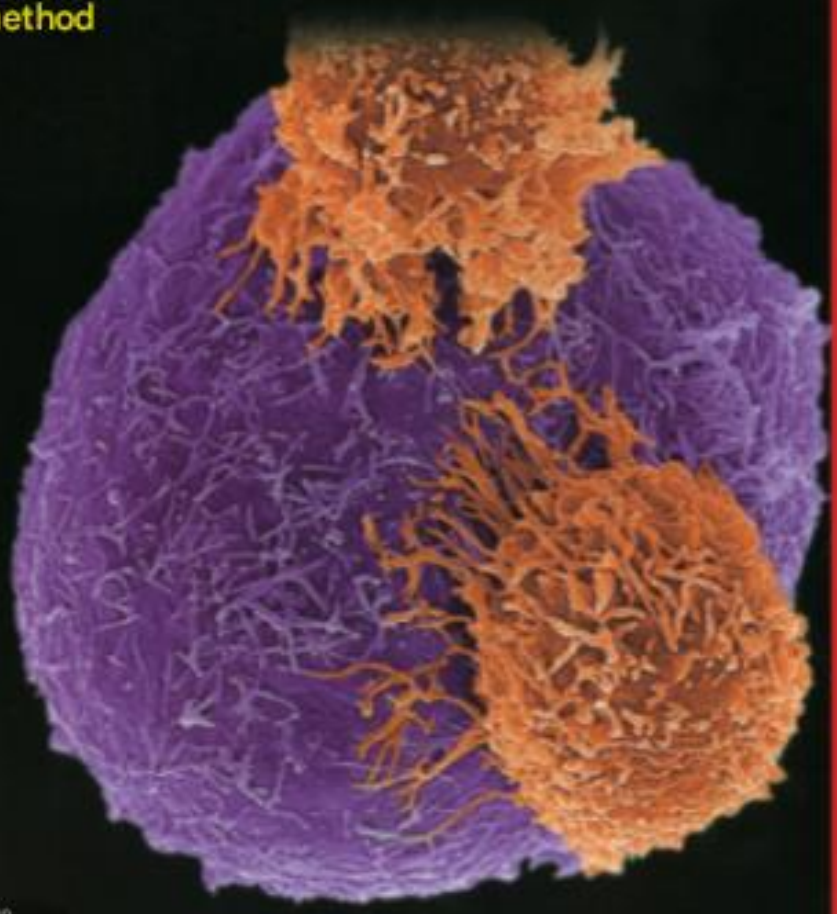
a customized treatment method

Cooperation with Noriya Ohno



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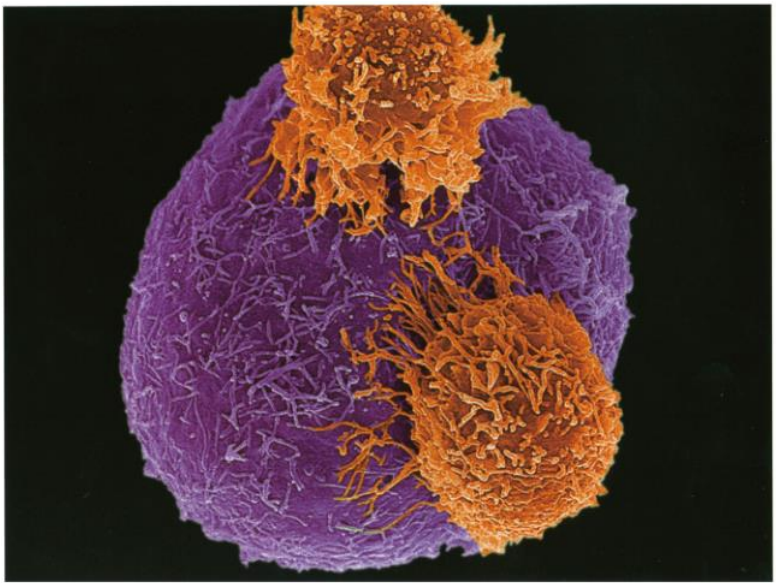
The forefront of cancer immunotherapy

1. Use your own cells to defeat cancer, a customized treatment method

Surgery, chemotherapy, and radiotherapy are known as the three major treatments for cancer. As the fourth treatment method, "cancer immunotherapy" is now attracting widespread attention. The strategy of cancer immunotherapy is to use the patient's own cells existing in the patient's body to target cancer cells. This article reports on the latest cancer immunotherapy developed by Harvard University in the United States and clinical research being promoted in the United States and Japan.

cooperate:
Donald Cave, Professor, Dana-Farber Cancer Institute, Harvard University
Noriya Ohno , Professor Emeritus, Jikei University School of Medicine



The patient's own immune cells, "killer T cells" (orange), entangle cancer cells (purple) and attack them (electron microscope image. The colors are obtained by dyeing). Cancer cells attacked by killer T cells die by cell suicide, or "apoptosis."

"The possibility of curing cancer has increased significantly compared to before. Because we can now obtain drugs and vaccines that regulate immune function, it becomes possible to control the patient's own immune system and eliminate cancer cells."

Harvard University's Dana-Farber Cancer Institute is widely known as one of the world's important bases for cancer research. Professor Donald Cave, who is promoting the research and development of the latest cancer treatment methods here, said this in an interview with Newton.

In recent years, Professor Cave has focused on promoting the research and development of "cancer immunotherapy". Cancer immunotherapy is a treatment method that flexibly utilizes the mechanism of cells in the body to eliminate foreign substances, that is, the "immune" mechanism, to eliminate cancer cells.

2. The fourth treatment after surgery, anticancer drugs, and radiation

Cancer is the process in which cancer cells that have lost their normal functions grow in the body and multiply to form tumors. The three major treatments for removing cancer tumors are surgery, chemotherapy, and radiotherapy.

Surgery is a method of directly operating on the patient's body to directly remove the cancer cells in the affected area. Chemotherapy is a method of using drugs (anticancer drugs) to block the life activities of cancer cells and cause damage to cancer cells. Radiotherapy is the use of radiation to

Each of the three major treatment methods has its own advantages and disadvantages. For example, if surgery can completely remove all cancer cells, it is expected to cure cancer. However, if the cancer tissue is small or the cancer cells have metastasized to various parts of the body, it is very difficult to remove it. Moreover, although chemotherapy and radiotherapy can kill cancer cells that cannot be removed by surgery, they can also cause damage to normal cells, and the adverse reactions caused by this are worrying. It is not uncommon for people to want to eliminate cancer cells but end up with huge adverse reactions, which in turn causes the most important patient's physical strength to decline.

Under such circumstances, the "cancer immunotherapy" that the world's cancer researchers, led by Professor Cave, have worked hard on is highly anticipated. In fact, abnormal cells that may become cancer cells in the future appear in our bodies every day. Even so, the reason why we don't get cancer immediately is that everyone has immune cells in their bodies that can detect these abnormal cells early and eliminate them. Artificially enhancing the role of these immune cells (activation) and allowing them to target and attack cancer cells lurking in every corner of the body is the idea of cancer immunotherapy. Because it uses one's own cells, it can be a treatment with few adverse reactions and avoid recurrence.

(left) The Dana-Farber Cancer Institute at Harvard University in Boston, USA. It is renowned as one of the world's leading cancer research centers.

(right) Professor Donald Cave answers Newton’s interview. As the leader of the Department of Translational Pharmacology and the Early Care Clinical Unit at Harvard University’s Dana-Farber Cancer Institute, he is committed to the development and clinical research of a variety of advanced treatments, including cancer immunotherapy.

3. Cancer treatment has improved due to the emergence of "antibody drugs"

As a treatment that uses the immune system in recent years, Professor Cave first proposed the use of "antibody drugs". Antibody drugs refer to the use of molecules (antibodies) that bind to specific proteins contained in cancer cells, which inhibit the proliferation of cancer cells and allow the body's immune cells to attack cancer cells. Professor Cave said.

" One striking example is Herceptin, which targets the Her2 protein, which is present in excess in one out of every three women with breast cancer . Herceptin not only acts directly on cancer cells to inhibit their proliferation, but also activates the body's immune response to kill cancer cells . "

based on antibody drugs such as Herceptin is also called "targeted therapy" because it targets proteins unique to cancer cells. What is the difference between this targeted therapy and conventional chemotherapy (anti-cancer drugs)? Professor Cave gave the following answer.
"Chemotherapy not only targets cancer cells, but also inhibits the proliferation of normal cells and kills normal cells. But targeted therapy is not like this. Because it uses molecules unique to cancer cells as targets, it can only inhibit the proliferation of cancer cells and only kill cancer cells."

Professor Cave also mentioned one of the important advances in the field of antibody drugs in recent years, the emergence of "CTLA-4 antibody". CTLA-4 is a protein that can act as a brake on the immune system by binding to immune cells T cells. CTLA-4 antibody can make this protein ineffective. In this way, the immune response in the body is activated, and the cancer cells are eliminated.

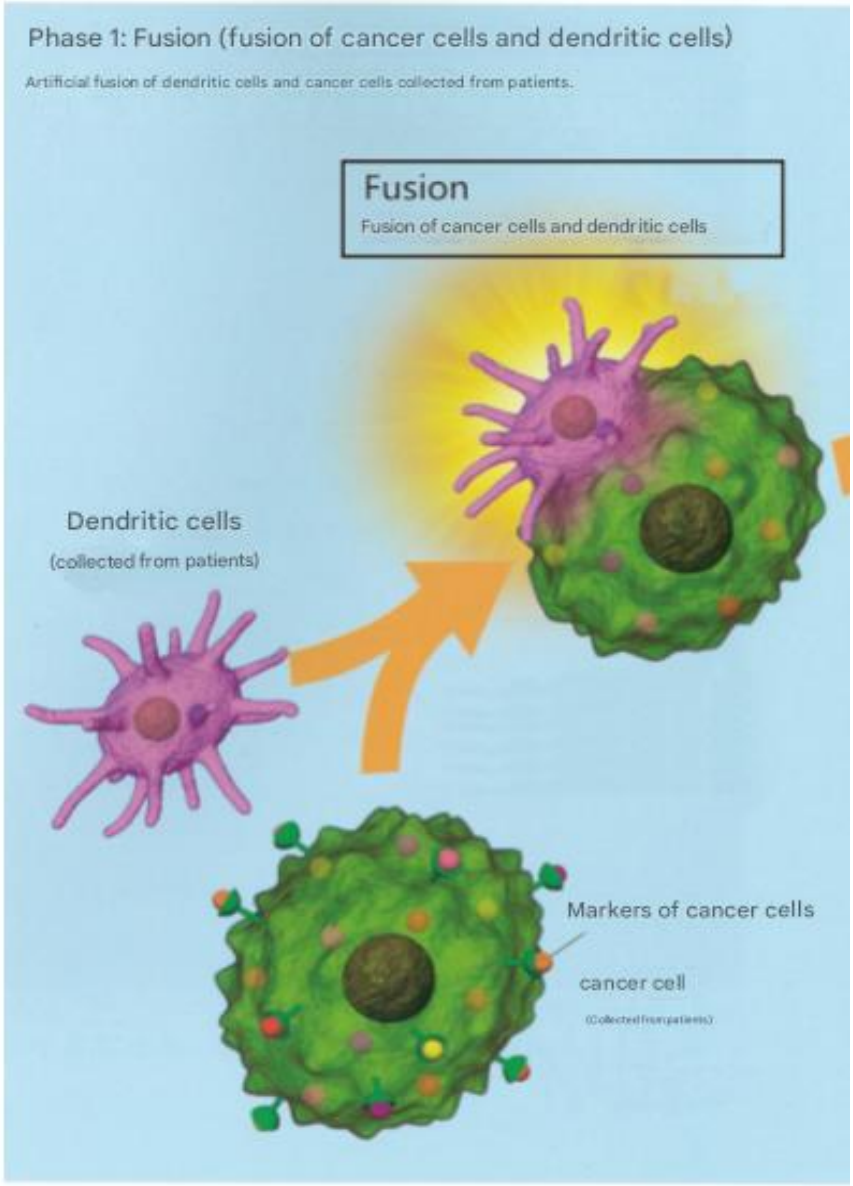
4. The latest cancer immunotherapy using "fusion cells"

The process of immunotherapy using fusion cells of dendritic cells and cancer cells developed by Professor Cave's team is shown on the right. In the first stage, cancer cells and dendritic cells are fused. In the second stage, the fused cells act as instructors to educate the cytotoxic T cells in the body. In the third stage, the educated cytotoxic T cells attack the cancer cells, killing them.

5. Collaborative efforts of dendritic cells and killer T cells

These targeted therapies generally show good results in cases where the characteristics of the cancer cells to be attacked are clear. However, depending on the patient, there are cases where the characteristics of the cancer cells to be attacked are not clear. If it is not clear what kind of protein the cancer cells contain, it is difficult to choose a treatment using antibody drugs.

As a means to break this limitation, the "immunotherapy using dendritic cells" that has attracted attention is being studied by cancer researchers around the world, led by Professor Cave. Dendritic cells are a type of immune cell, named for the many branch-like protrusions on their surface. Dendritic cells usually patrol and guard every part of the body without missing any. Once they find abnormal cells such as virus-infected cells and cancer cells, they swallow them into the dendritic cells and decompose and remove them.



The work of dendritic cells is not over yet. Dendritic cells will present the protein fragments obtained by decomposing abnormal cells on their own cell surface. And they will educate other immune cells around them about the characteristics of abnormal cells, as if saying "attack cells with this mark". This work, called "antigen presentation", is an important function of dendritic cells.

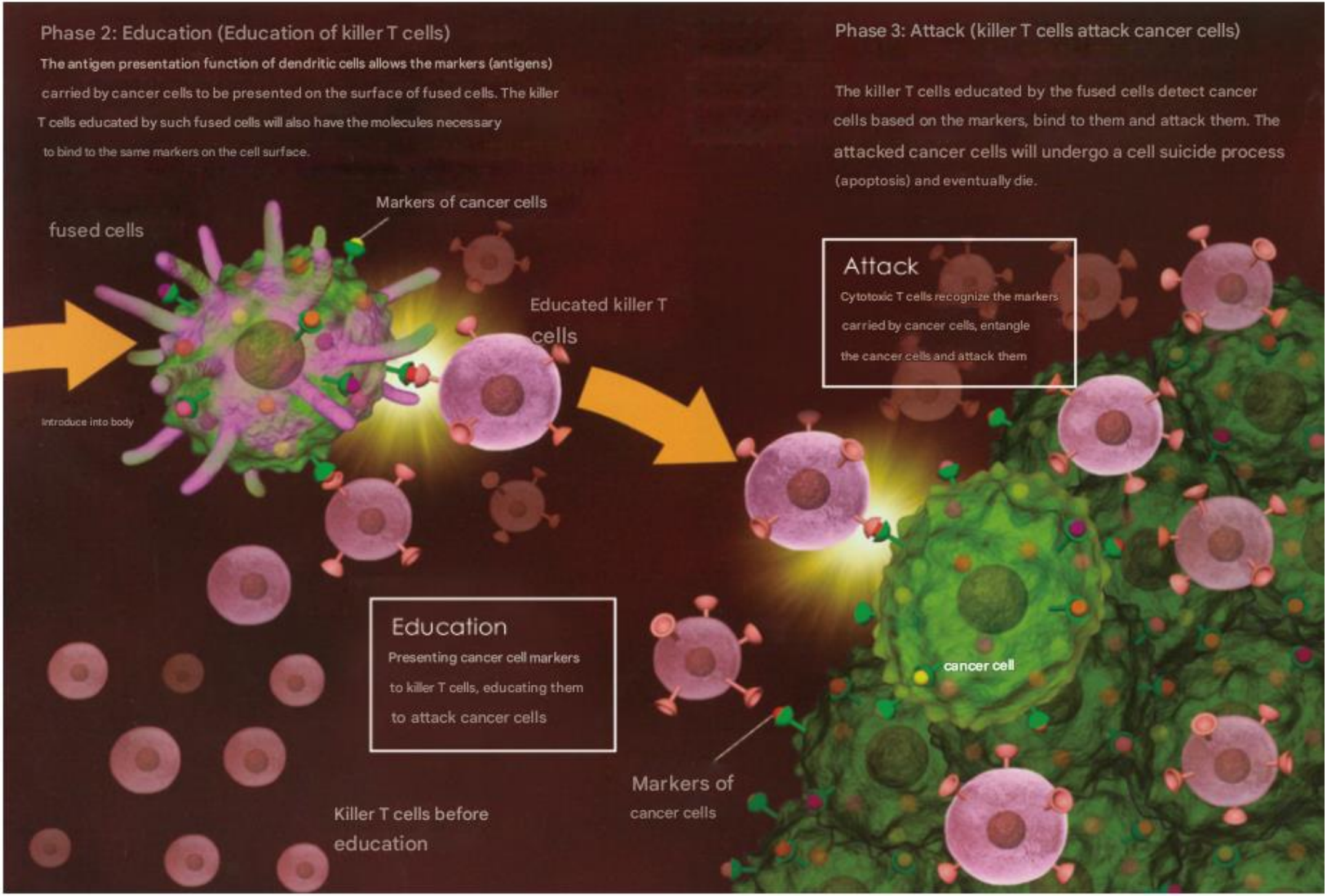
In the treatment method called "cancer peptide vaccine therapy" promoted by the National Institute of Science, Kurume University , etc., several to dozens of protein fragments (peptides) carried by the patient's cancer cells are administered to the patient and used as markers to educate immune cells.

On the other hand, the method that aims to implement education more effectively is the "fusion cell therapy" established by Professor Cave. In this method , dendritic cells taken from the patient's body are fused with cancer cells taken from the patient's body in vitro, and the fused cells are returned to the patient's body. In this way, the fused cells act as instructors and can teach the characteristics of cancer cells to the cytotoxic cells without omission (please refer to the following illustration for details).

The immune cells that are educated by dendritic cells are called "killer T cells". As the name "killer" suggests, the killer T cells educated by dendritic cells will find abnormal cells to attack, bind to them, and induce the cell's suicide phenomenon, that is, "cell apoptosis", causing its death. The use of dendritic cell immunotherapy to eliminate cancer cells by this coordinated combat between dendritic cells and killer T cells is called dendritic cell immunotherapy.

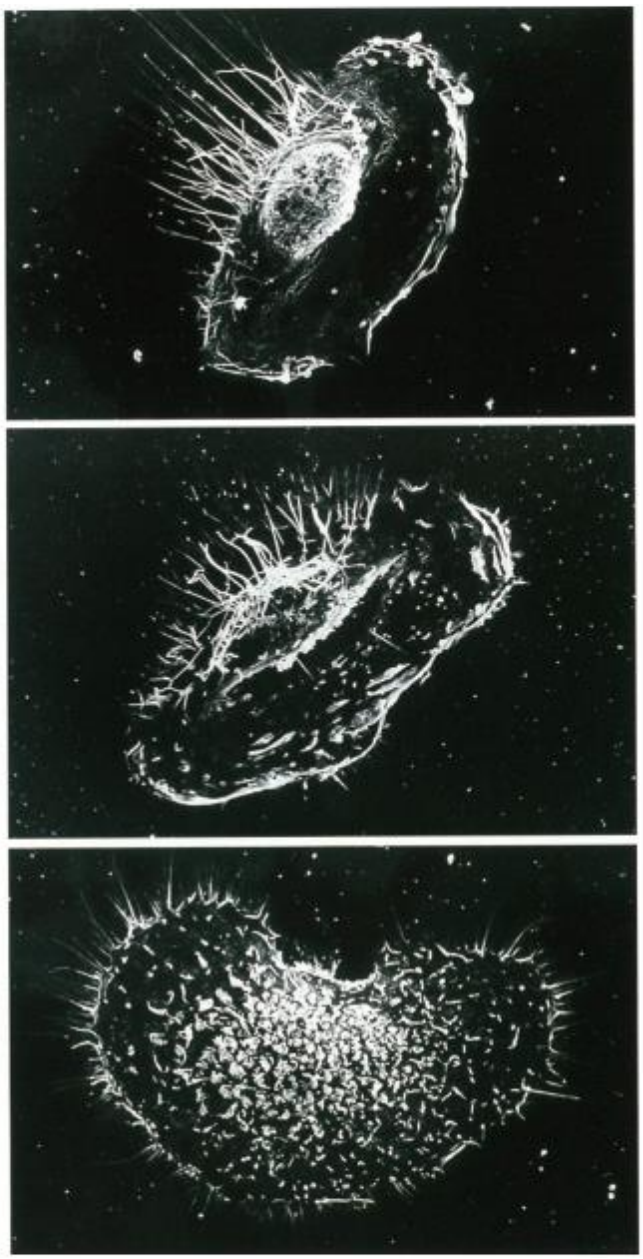
In immunotherapy using dendritic cells, "how to present cancer cell markers on the surface of dendritic cells and effectively educate cytotoxic T cells" is a key.

Professor Cave said: "In this technique, dendritic cells, which are extremely powerful immune cells, are fused with cancer cells. The resulting fused cells can produce all the markers of cancer cells and have the function of triggering an immune response. These fused cells are then returned to the patient's body."


Phase 2: Education (Education of killer T cells)
The antigen presentation function of dendritic cells allows the markers (antigens) carried by cancer cells to be presented on the surface of fused cells. The killer T cells educated by such fused cells will also have the molecules necessary to bind to the same markers on the cell surface.
Phase 3: Attack (killer T cells attack cancer cells)
The killer T cells educated by the fused cells detect cancer cells based on the markers, bind to them and attack them. The attacked cancer cells will undergo a cell suicide process (apoptosis) and eventually die.
Markers of cancer cells
fused cells
Educated killer T cells
Introduce into body
Attack
Cytotoxic T cells recognize the markers carried by cancer cells, entangle the cancer cells and attack them
Education
Presenting cancer cell markers to killer T cells, educating them to attack cancer cells
cancer cell
Markers of cancer cells
Killer T cells before education

6. Improved version is also available, clinical research is being conducted in the US and Japan

The fusion cell therapy developed by Professor Cave's team has been further improved by Dr. Noriya Ohno, Professor Emeritus of Tokyo Jikei University of Medicine, who has been conducting research with Professor Cave for many years.



The process until cell fusion is complete

(Top) One hour after the start of fusion, cancer cells collected from a patient (larger cells in the center) come into contact with smaller cells on dendritic cell processes.
(Middle) 2 hours after the start of fusion. Fusion of the two cells is ongoing.

(Bottom) 4 hours after the fusion began. The result of the fusion of cancer cells and dendritic cells is that they look like a large dendritic cell. All images are provided by Dr. Ohno.

" The improvement made by Dr. Ohno is to use not only the fusion cells of cancer cells and dendritic cells, but also to administer a substance called "interleukin 12" to the patient at a predetermined time point to further activate the immune cells. Interleukin 12 is known as a chemical substance (collectively called cytokine) that immune cells release when they detect abnormal cells such as cancer cells and virus-infected cells in order to activate other immune cells in the surrounding area. Dr. Ohno had experience in the past trying to develop interleukin 12 as a cancer treatment drug alone, and that experience is closely related to this improvement.
The improved fusion cell therapy is currently undergoing clinical research in Japan and the United States. According to Dr. Ohno's research, 4 out of 15 patients who have received this treatment so far have seen a significant reduction in cancer cells. If we include cases with limited therapeutic effects, the number of cases where the therapeutic effect can be recognized is 8 out of 15.

However, Dr. Ohno said that in the remaining seven cases, the treatment failed to prevent the further development of cancer. "Unfortunately, this immunotherapy method is not covered by health insurance and has not become the first choice for cancer treatment. The 15 people who participated in our clinical study were all patients who had undergone three major treatments, surgery, chemotherapy, and radiotherapy, and their symptoms did not improve. More than half of them were observed to have a therapeutic effect, so it can be said that this is a groundbreaking event."

7. Cancer immunotherapy moves towards the “6th generation”

Cancer immunotherapy actually has a long history. Cancer immunotherapy began with drugs called "immunoenhancers" that appeared in the 1970s . Immunoenhancers are a type of drug that is believed to have the effect of activating the body's immune system . For example, it is said that injecting "picibanil " made from dried hemolytic streptococci into the body can activate immune function. Dr. Ohno calls this treatment using immunoenhancers the first generation of cancer immunotherapy.

In the 1980s, the second generation of "cytokine therapy" was introduced by Dr. Ohno. Cytokines are chemical substances released by immune cells to communicate with each other, such as "interferon" and "interleukin". Cytokine therapy is to inject such cytokines into the patient's body to enhance the immune system's ability to fight cancer cells.

Cases for Lung Cancer:

Patient 1: Male, 60+, physician, Stage IV lung adenocarcinoma

- **2013**
  - Jun: Detected lung shadow via biopsy → confirmed adenocarcinoma
  - Jul: Ineligible for surgery; started **chemotherapy (carboplatin + vinorelbine, 5 cycles) + radiotherapy (60Gy)**
  - Dec: Gamma knife for brain metastases
- **2014**
  - Mar: EGFR mutation-positive → began **gefitinib (Iressa)**
  - Apr: Repeat gamma knife for brain metastases
  - May: Received **peptide cancer vaccine** at a university hospital
- **2015**
  - Mar: Multiple brain metastases → whole-brain irradiation
  - Aug: Started **fused cell vaccine**
- **2016**
  - Jan: Small cerebellar metastasis (resolved by Apr)
- **2017**
  - Jul: Initiated **PD-1 (nivolumab)**, ongoing (3 doses)
- **Current Status**: Stable, plans to continue fused cell vaccine intermittently

Patient 2:

Patient: Male, 40+, Stage IV, lymph node & adrenal metastases

- **2015**
  - Jul: Diagnosed with lung adenocarcinoma, right cervical lymph node and bilateral adrenal metastases (inoperable, EGFR wild-type)
  - Sep: Began **fused cell vaccine** prep
  - Oct: Combined **chemotherapy (carboplatin + pemetrexed) + fused cell vaccine**
  - Dec: Rapid decline in tumor markers; significant shrinkage of lymph nodes/adrenal lesions (noted as "remarkable" by physicians)
- **2017**
  - May: Residual lesions → **single PD-1 (nivolumab) dose** achieved complete remission

Patient 3:

Patient: Male, 60+, Stage I

- **2018–2019**
  - Nov: Diagnosis
  - Jan: **Radiotherapy + fused cell vaccine** (1st infusion)
  - CT showed tumor shrinkage → completed 6-course vaccine regimen
  - Jun: PET/CT confirmed near-complete resolution; tumor markers normalized
  - Received 7th booster dose
- **Outcome**: Successful combination therapy; patient resumed travel