

# CARCI Immune Cell Therapy A New Choice for Cancer Treatment

# Center of Stem Cells and Precision Medicine, Hualien Tzu Chi Hospital

By Huang Szu-Chi, Chiang Chia-Yu





Cancer treatment research has opened up new opportunities in the field of oncology in recent years. Major breakthroughs in the treatment of leukemia and lymphoma with CAR-T cell therapy have drawn wide attention. In September 2022, the research team of the Center of Stem Cells and Precision Medicine at Hualien Tzu Chi Hospital partnered with Novartis, one of the top pharmaceutical companies in the world, in the adoption of Chimeric Antigen Receptor T-cell Therapy (commonly known as CAR-T Immune Cell Therapy), a new innovative cancer therapy developed in America and Europe. Six months after adoption of this groundbreaking new therapy, Hualien Tzu Chi Hospital successfully treated the first patient with CAR-T cell therapy. This success story represents a beacon of hope for leukemia and lymphoma patients in Taiwan and Asia who intend to seek new forms of treatment.

#### Chimeric Antigen Receptor T-cell Therapy - A New Weapon in the Fight Against Cancer

Chimeric Antigen Receptor T-cell Therapy (CAR-T) marks one of the biggest breakthroughs in oncology in recent years and gives hope for a new lease of life to a large number of recurrent cancer patients. CAR-T therapy requires the separation of T-cells from the blood of patients. These cells are re-engineered by adding a gene for a receptor



Hualien Tzu Chi Hospital Cell Therapy Center officially presents the achievements of the first application of CAR-T therapy in eastern Taiwan on July 4, 2023.



that can identify cancerous cells. The goal is to transform T-cells into CAR-T cells that are capable of recognizing antigens on the surface of cancer cells. Upon cultivation and proliferation of these cells in a professional laboratory, this "Living Drug" is reinjected into the patient's body to activate these genetically modified, police-like T-cells and transform them into specially trained "Robocops". CAR-T cells have the ability to accurately identify the enemy and are more potent in eliminating





Upon high-precision treatment by the Precision Medicine & Stem Cell Manufacturing Center of Hualien Tzu Chi Hospital, the patient's T-cells were transported to the laboratory of Novartis HQ in Switzerland by special flight on March 27, 2023, to produce the life-saving CAR-T cell drug.

the threat posed by cancerous cells. Dr. Li Chi-Cheng, Director of the Center of Stem Cells and Precision Medicine at Hualien Tzu Chi Hospital, points our that "CAR-T therapy incorporates key characteristics and benefits of gene, cell, and immunotherapy, the three most advanced areas of medical technology."

CAR-T therapy, a novel treatment method which has been approved by the US Food and Drug Administration (FDA), can be applied to hematological neoplasms including leukemia, lymphoma, and multiple myeloma. Director Li notes that CAR-T therapy was administered for the first time in America. The first patient who received CAR-T therapy was a 6-year-old girl named Emily, who suffered from acute lymphoblastic leukemia (ALL). After undergoing treatment for 11 years since 2012, her cancer has not recurred. and she is completely healthy. Every year, she posts a picture of herself, announcing to everyone that she has been cancer-free for another year. In Taiwan, the Ministry of Health and Welfare approved the adoption of CAR-T immune cell therapy at the end of 2021. Only Hualien Tzu Chi Hospital, NTU Hospital, and China Medical University Hospital are currently capable of administering this therapy and have done so with success.

Dr. Lin Shinn-Zong, Superintendent of Hualien Tzu Chi Hospital, exclaims that "Hualien offers new hope for cancer patients!" In view of the fact that cancer has topped the list of leading causes of death in Taiwan for many consecutive years, this exclamation reflects the commitment of healthcare professionals to pursuing the highest standards and the most heartfelt blessings to cancer patients. Hualien Tzu Chi Hospital is steadfastly committed to caring for the health of all citizens through medical services in all branches and persists in its efforts to pursue innovation and progress in the treatment of critical illnesses. The medical team makes an all-out effort to bring new hope to cancer patients and their family members.

#### Ninth Case Nationwide – First Case of CAR-T Treatment in Eastern Taiwan

Following the adoption of Novartis CAR-T Cell Therapy in 2022, the cell therapy team of Hualien Tzu Chi Hospital initiated CAR-T treatment for a lymphoma patient Dr. Chou, the first case of CAR-T treatment in eastern Taiwan and the ninth case nationwide. One month after infusion with CAR-T cells, the team conducted precise tracking through Positron Emission Tomography (PET) which revealed that the cancer cells had completely disappeared.

Director Li points out that the first patient who underwent CAR-T treatment at Hualien Tzu Chi Hospital was none other than Dr. Chou, who once served at the Division of Medical Imaging of Hualien Tzu Chi Hospital. In 2018, Dr. Chou was diagnosed with an extremely rare form of lymphoma-leukemia cancer. In July of the same year, he underwent allogeneic hematopoietic stem cell transplantation from a non-relative donor. However, his lymphoma recurred five years later. In February 2023, he was re-examined and diagnosed with "Triple-hit Lymphoma", one of the most difficult-to-treat forms of cancer. The medical team concluded that the chances of curing this aggressive form of cancer with a second hematopoietic stem cell transplantation were very slim.

In 2018, the year of disease onset, Dr. Chou was still serving as a clinical physician. He recalls feeling extremely exhausted after performing surgery for embolism and having to lie down to rest. When his colleagues saw him lying there motionless, they immediately took him to the emergency department. He still remembers the emergency room doctor saying with a grave look on his face "Dr. Chou, your blood cells look unusual." At that moment, he knew it was much more serious than a mere flu as he originally suspected. He was wondering if it could be a blood neoplasm.

Subsequently, Dr. Chou started to experience bone pain all over his body. Luckily, a perfect, non-relative genetic match was found in the Buddhist Tzu Chi Stem Cells Center database only two months after initiation of targeted therapy and intrathecal chemotherapy. He therefore underwent allogeneic hematopoietic stem cell transplantation from a non-relative donor paired with a complementary traditional Chinese medicine therapy. After regaining his physical health, he chose to temporarily leave the medical center and accept a position at a smaller hospital with a lower workload. This gave him a chance to continue to pursue his desired medical career while planning a venture into the field of medical education and passing on of professional experiences.

He initially thought that there was a chance of full recovery almost five years after the transplantation. However, he was in for a shock when he felt a little lump on his left chest wall after the Lunar New Year season in 2023. This lump quickly grew and reached a size of over 7 cm within only one week. After a biopsy, it was confirmed that the lymphoma had returned. Dr. Huang Wei-Han, Deputy Director of the Division of Immunotheraphy states that Dr. Chou was diagnosed with Triple-Hit Diffuse Large B-cell Lymphoma (DLBCL), which is the most malignant expression of three different genetic rearrangements, in February 2023. He further points out that "there was no cure for this form of lymphoma in the past. CAR-T therapy offers a considerable chance for successful treatment of this aggressive cancer."

## Concerted Effort to Manifest Positive Energy – Down-to-Earth Precision Medicine Practices

Saving lives brooks no delay. Director Li Chi-Cheng therefore made a prompt decision. After confirming that there were no signs of cancer recurrence in the patient's bone marrow and that the immune T-cells in his body were still the healthy hematopoietic stem cells of the original donor, the medical team of Hualien Tzu Chi Cell Therapy Center extracted the weakened T-cells from the blood of Dr. Chou in a prompt manner on March 10. Upon high-precision treatment and freezing by the Stem Cell Manufacturing Center of Hualien Tzu Chi Hospital, the patient's T-cells were transported to the laboratory of Novartis HQ in Switzerland by special flight on March 27. The cells



Upon re-engineering of the patient's T-cells, the CAR-T cell medication Kymriah® was sent back to Hualien Tzu Chi Hospital on April 24, 2024.





were then genetically modified over a period of roughly one month to produce the life-saving CAR-T cell drug Kymriah® (scientific name: Tisagenlecleucel). Upon arrival at Hualien Tzu Chi Hospital on April 24, Director Li Chi-Cheng, Deputy Director Huang Wei-Han, Dr. Sun Li-Yi (Director of the Stem Cell Manufacturing Center), and Dr. Chen Yi-Shan (Director of the Clinical Pharmacy Division, Department of Pharmacy) carried out verification and signed acceptance of the delivered bag which was filled with 26 cc of Kymriah®, containing 520 million CAR-T cells.

During the CAR-T cell re-engineering and cultivation process, the medical

team didn't slow down its pace and started to initiate salvage targeted drug and chemotherapy on March 17. Upon conclusion of chemotherapy, most tumors had shrunk significantly, but after less than a week, the cancerous cells had again grown to the size of a palm and the tumors had spread to the abdominal and chest wall area. Consequently, the medical team adopted a multi-pronged approach composed of a new targeted medication supplemented by chemo and radiation therapy with the hope of minimizing the size of the lymphoid neoplasms prior to CAR-T cell infusion. Due to emerging side effects, a Chinese medicine doctor was



Upon completion of verification procedures by medical, pharmacy, and nursing representatives, the team of the Stem Cell Manufacturing Center delivered the retrieved and unfrozen CAR-T cell medication Kymriah® to the transplantation ward on May 16 for infusion into the patient's body.

enlisted on the team to offer the patient an integrated Chinese and Western medicine therapy. The goal was to make the therapy process more bearable for the patient through traditional Chinese medicine conditioning.

Upon arrival of the vital CAR-T cell medication Kymriah® at Hualien Tzu Chi Hospital, Dr. Chou underwent chemotherapy prior to the cell infusion on May 11. For caution's sake, the infusion was carried out in the bone marrow transplantation isolation ward. At noon of May 16, Superintendent Lin ShinnZong brought Dr. Chou Jing Si Herbal "Kang Ru" Liquid Packet and "Yue Le" Powder Drink together with a big apple which symbolizes blessings in Taiwanese culture to convey his best wishes for a speedy recovery. The medical team and the Stem Cell Manufacturing Center acted in concerted to deliver the retrieved Kymriah® to the 21 East Bone Marrow Transplantation Ward. Upon completion of unfreezing and verification procedures, Dr. Huang Wei-Han, the attending physician and Deputy Director of the Division of Immunotherapy, injected the prepared



CAR-T cells into the patient's body at 1:30 pm.

Dr. Chou shares that the medical team explained to him after recurrence of his cancer that the survival rate of a second transplantation was extremely low. Even the so-called "Nine Deaths and Still Alive", which means narrow escape in Chinese, has a 10% survival chance, while he only had a 2% chance. Upon exhaustion of all treatment options including surgery, chemotherapy, targeted drug therapy, and electrotherapy, CAR-T therapy was his last hope.

### Weathering the Cytokine Storm through Protection -Unwavering Will to Survive

Upon completion of the infusion, the genetically modified CAR-T cells with greatly upgraded cancer-fighting potency started to initiate a series of immune reactions to combat the cancerous B-cells in the patient's body, which also resulted in some inflammatory reactions caused by metabolism of cells, which is commonly known as the cytokine storm or cytokine release syndrome (CRS). The medical team therefore administered Anti-IL-6 therapy. One month after the cell infusion, Dr. Chou's neutrophil, hemoglobin, and platelet counts remained stable. A total body PET (Positron Emission Tomography) scan revealed that the original neoplasms

were no longer visible. After gradually regaining his physical strength, Dr. Chou was able to engage in simple exercises accompanied by his wife.

Dr. Chou still recalls that a lot of coworkers and friends urged him to retire after they knew that he had contracted lymphoma and leukemia. However, he had made a vow to Bodhisattva in his heart that he would return to his post to protect lives after successful treatment of his cancer. After completion of the first therapy, he initially thought he was fully recovered and returned to the hospital to engage in medical education and passing on of experiences. He was taken aback when his cancer returned. Thinking back on his CAR-T therapy, he makes the following statement: "I'd like to extend my special gratitude to my wife for always being with me and taking care of me, to the Tzu Chi medical team for their perseverance and superb medical skills, and to a large number of familiar and unfamiliar virtuous individuals for their concern and encouragement. I still have this wish in my mind to return to my post and continue to protect lives and fulfill my mission of dedicating my professional knowledge and skills to helping people in need of medical assistance if I'm given a new lease of life."

Mrs. Chou expresses her deepest gratitude to Dharma Master Cheng Yen, the Tzu Chi Hospital hematological



Prior to the infusion, Superintendent Lin Shinn-Zong, Dr. Li Chi-Cheng, Director of the Center of Stem Cells and Precision Medicine (center), and Dr. Sun Li-Yi, Director of the Gene and Stem Cell Manufacturing Center (right) cheer up Dr. Chou by video conference.

neoplasm, cell therapy, and bone marrow transplantation teams, and Tzu Chi volunteer Yen Hui-Mei for her spiritual encouragement. She is overcome with emotion when thanking Hualien Tzu Chi Hospital for giving her husband two chances at a new life. Mrs. Chou is sincerely thankful to the Tzu Chi bone marrow database for locating a perfect genetic match for a hematopoietic stem cell donation and transplantation surgery and to the medical team for the successful administration of CAR-T Immune Cell Therapy. She shares that these "two hospital stays were long and taxing, resembling a super marathon. Luckily, the members of the medical team cared for my husband like a family member, and the other patients in the ward showed mutual concern and constantly encouraged each other. This not only gave us the strength to persevere but also explains the miraculous success of this therapy. We were extremely fortunate that Hualien Tzu Chi Hospital had already forged a partnership with Novartis when my husband's cancer recurred, which gave him an opportunity to undergo CAR-T Immune Cell Therapy."



In deep appreciation of the efforts of all involved teams, Mrs. Chou states emotionally that "I am very aware of my husband's passion for medical care, and I sincerely hope that he can serve even more patients after his full recovery."

#### A Major Milestone in Cell Therapy

Dr. Lin Shinn-Zong, Superintendent of Hualien Tzu Chi Hospital, says that a lymphoma diagnosis is an enormous physiological and psychological burden for the patient, his/her close family members, and the whole family. In addition to refining traditional treatment techniques, medical teams therefore do their utmost to identify novel treatment methods that are more suited to the needs of the patients. The adoption of the CAR-T therapy by Hualien Tzu Chi Hospital gives new hope for cancer cure to patients and their family members.

The successful completion of the first CAR-T therapy in eastern Taiwan not only indicates that Hualien Tzu Chi Hospital is on a firm footing in the field of cell therapy but also marks a major milestone in cancer care in Taiwan. Director Li Chi-Cheng points out that CAR-T Immune Cell Therapy is a one-off treatment, which requires infusion of live T-cells back into the patient's body. This "Living Drug" is capable of ongoing growth in vivo and manifests powerful anti-cancer effects.



Dr. Huang Wei-Han, the attending physician and Deputy Director of the Division of Immunotherapy, injects the prepared CAR-T cells into the patient's body.

It exhibits a cure rate of around 40% in terminal patients with hematological neoplasms. Hualien Tzu Chi Hospital carefully selected the most opportune time for extraction of T-cells from the patient's body for the first administration of CAR-T therapy in eastern Taiwan. The hostile cancer cells were attacked at the moment of strongest immunity. This novel therapy not only helps prolong patient lives but will also serve as a source of inspiration for cell therapy applications by medical practitioners in Taiwan. It is our sincere hope that all healthcare professionals will make a concerted effort to develop new choices and bring new hope for cure to patients afflicted by difficult-to-treat cancers.