

News Release



November 11, 2021

Center for iPS Cell Research and Application (CiRA), Kyoto University
National Cancer Center Japan (NCC)
Japan Agency for Medical Research and Development (AMED)

First in-patient transplantation of iPS cell-derived natural killer cells to treat ovarian cancer

Main Points

- Natural killer cells prepared from iPS cells were transplanted into an ovarian cancer patient
- The iPS cells were provided by the CiRA Foundation
- The trial is being conducted at the NCC Hospital East

1. Summary

The Center for iPS Cell Research and Application (CiRA), Kyoto University, and the National Cancer Center (NCC) Hospital East are cooperating on a phase I clinical trial to investigate the safety and tolerance of a new iPS cell-based adoptive cellular therapy (ACT) for ovarian cancer. The iPS cells were used to generate chimeric antigen receptor (CAR) innate lymphoid/natural killer cells (ILC/NK) targeting glypican-3 (GPC3) protein, which, for the first time, have been transplanted into a patient. CiRA Professor Shin Kaneko is leading the project.

ACT using CAR T cells and CAR NK cells has exceptional promise against cancer. Prof. Kaneko has combined CAR technologies with iPS cell technology to increase the number of patients who can benefit from this treatment. iPS cells with homologous human leukocyte antigens (HLA) especially are immunologically compatible with a larger number of patients. Genetic engineering of the iPS cells makes the ACT more potent.

GPC3 is an attractive target because its expression specifically correlates with several cancer cells including ovarian cancer cells. The researchers therefore genetically engineered HLA-homozygous iPS cells to express the GPC3 receptor and then differentiated the cells into NK cells for ACT.

The clinical trial began in April, and the cells were transplanted into the first patient in September.

2. Key Dates

January 25, 2021	NCC Institutional Review Board approves the plan
March 12, 2021	The plan is submitted to the Japan Pharmaceutical and Medical Devices Agency (PMDA)
April 12, 2021	The clinical trial begins
September 2021	The first transplantation to a patient is administered

3. Clinical Trial Outline

(1) Name of clinical trial

A phase 1 clinical trial of intraperitoneal administration of GPC3-CAR expressing iPS cell-derived innate lymphoid/natural killer cells for patients with GPC3 positive advanced ovarian clear cell carcinoma with peritoneal dissemination

(2) Purpose of clinical trial

To evaluate the safety and tolerance of repeated intraperitoneal injections of anti-GPC3 expressing CAR iPS cell-derived ILC/NK cells, or iCAR-ILC-N101, in patients with inoperable ovarian cancer.

(3) Cells used in the clinical trial

The iPS cell line, QHJI01s04, provided by the CiRA Foundation through its iPS cell stock, was genetically engineered and differentiated into iCAR-ILC-N101.

(4) Target disease

Patients with inoperable and advanced ovarian follicular carcinoma expressing GPC3.

(5) About the cell transplantation

Approximately 1×10^6 iCAR-ILC-N101/kg are transplanted weekly for four weeks percutaneously into the peritoneal cavity. In total, the minimum and maximum doses are 0.5×10^6 and 3.0×10^6 iCAR-ILC-N101/kg, respectively.

(6) Number of patients

6-18

(7) Implementation date

April 12, 2021 – March 3, 2024

(8) Patient recruitment

For details about patient recruitment, see the NCC Hospital East site (in Japanese).

https://www.ncc.go.jp/jp/ncce/division/clinical_trial/ctas/patient/list/ovarian/006.html

4. Participating organizations

○CiRA

- Development of cells for clinical trial
- Methods for cell manufacturing and quality control
- Non-clinical safety studies

Principal investigator: Shin Kaneko

○National Cancer Center Japan

- Preparation of investigator-initiated clinical trial plan
- Implementation of trial

Coordinating physicians:

National Cancer Center Hospital East

Department of Experimental Therapeutics/Deputy Director

Toshihiko Doi

Department of Experimental Therapeutics/Department of Medical Oncology

Kenichi Harano

Department of Experimental Therapeutics/Department of Hematology

Junichiro Yuda

Clinical Research Support Office

Akihiro Sato

National Cancer Center Exploratory Oncology Research & Clinical Trial Center

Division of Cancer Immunotherapy

Tetsuya Nakatsura

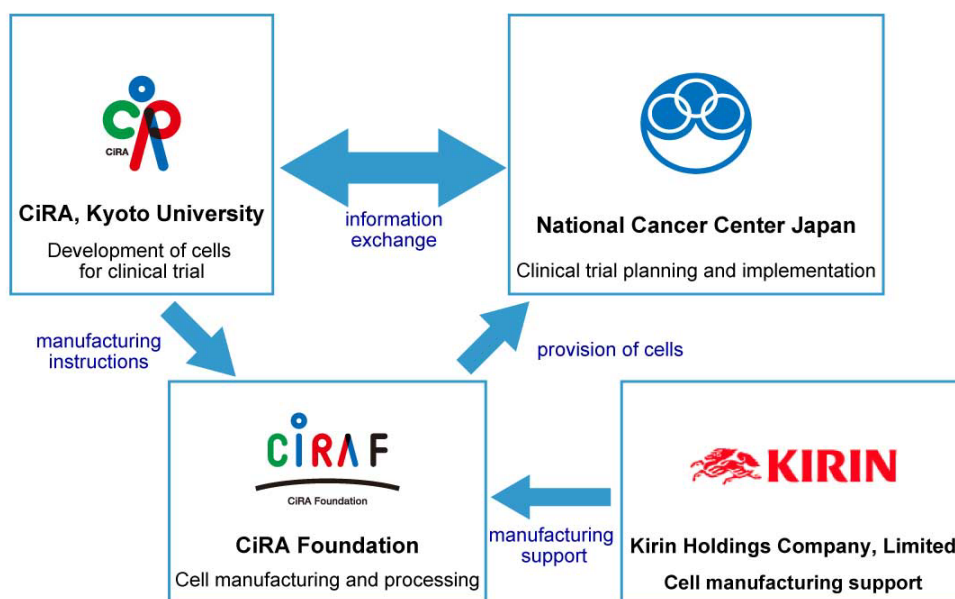
○CiRA Foundation

- Manufacturing of cellular products
- Validation of manufacturing
- Validation of analysis

○Kirin Holdings Company, Limited

- Support for manufacturing of cellular products

Organization flow chart



5. Funders

This research is supported by the following organizations.

- The Japan Agency for Medical Research and Development (AMED)

6. Key terms

1) Natural killer (NK) cells

A type of cell in the innate immune system, NK cells do not respond to any specific antigens of a pathogen or cancer but rather to conditions such as cell injury.

2) iPS cell stock

The iPS cell stock at the CiRA Foundation is a collection of iPS cell lines made from HLA-homologous healthy donors available for regenerative medicine. The project began in 2013 at CiRA but was passed to the CiRA Foundation in 2020. Currently, the stock includes 27 cell lines from 7 donors and is immune compatible with 40% of the Japanese population. Through genome editing, the CiRA Foundation plans to add new iPS cell lines to increase the percentage of the compatible population.

3) Chimeric antigen receptors (CAR)

CAR are receptors that have been added to the surface of immune cells by genetic engineering. The CAR is selected based on the antigen expression of the targeted cancer cell and allows the immune cells to bind and attack this target.

4) ILC/NK

Innate lymphoid cells (ILC) are immune cells different from T cells in that they are activated independent of an antigen. However, different subsets of ILC express similar master transcription factors and cytokine profiles as different subsets of T cells. NK cells correspond to CD8 killer T cells, type 1 ILCs to type 1 CD4 helper T cells, type 2 ILCs to type 2 CD4 helper T cells, and type 3 ILCs to type 17 CD4 helper T cells. NK/ILC is a type of cell made from iPS cells that have characteristics of both ILC and NK cells.

5) HLA-homozygous iPS cells

Human antigen leukocytes (HLA) are expressed by almost all cells in the body and are used by the immune system to recognize “self” cells versus pathogenic cells. Two HLA are inherited by both parents, one from each; HLA homozygosity states that the two inherited HLA are the same. Probabilistically, HLA-homozygous cells immune-match a larger population for transplantation.