

**Japan Tissue Engineering, Nagoya University, and Shinshu University
sign patent license agreement for the development of a low-cost manufacturing technology for
autologous CAR-T cell therapy with enhanced targeting efficiency against CD 19-positive acute
lymphoblastic leukemia**

June 21, 2018

Japan Tissue Engineering Co., Ltd.

Nagoya University

Japan Tissue Engineering Co., Ltd. (a Fujifilm Group company; President: Ken-ichiro Hata, “J-TEC”, hereafter) and Nagoya University (President: Seiichi Matsuo) announced a three-party patent license agreement between J-TEC, Nagoya University, and Shinshu University (President: Kunihiro Hamada) to develop a low-cost manufacturing technology for genetically modified autologous (¹) T cells (CAR-T cells) with enhanced targeting efficiency against cancer, as a therapy for CD19²-positive acute lymphoblastic leukemia (ALL)³. This manufacturing technology, jointly developed⁴ by groups led by Professor Yoshiyuki Takahashi, Department of Pediatrics, Nagoya University and Professor Yozo Nakazawa, Department of Pediatrics, Shinshu University, is a ground-breaking technology that is expected to contribute to the spread of CAR-T therapy which is drawing attention as a new cancer therapy.

Based on the agreement, J-TEC will acquire the exclusive rights to develop, manufacture, and commercialize in Japan the autologous cell-derived therapies targeting CD 19-positive ALL using this technology. Nagoya University and Shinshu University will receive an upfront payment upon signing of the agreement, as well as payments at development milestones and royalties from J-TEC based on sales.

CAR-T therapy is an immune cell therapy using CAR-T cells, which are genetically modified T cells⁵ with enhanced targeting efficiency against cancer. Two therapies using autologous CAR-T cells have already been approved in the U.S. and have been confirmed to have high therapeutic efficacy.

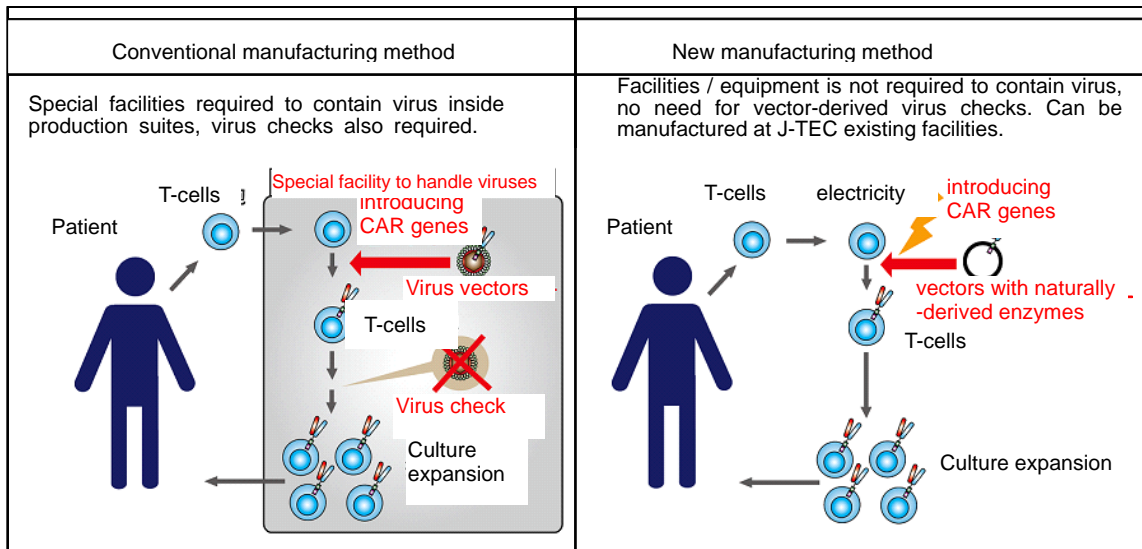
It is common to use viral vectors⁶ for introducing CAR genes⁷ into T cells collected from the blood when making CAR-T cells. However, there are issues with this method, such as the high cost of viral vectors and the facilities/equipment required to contain viruses to ensure safety, leading to high manufacturing costs.

The CAR-T cell manufacturing technology jointly developed by Nagoya University and Shinshu University does not use conventional viral vectors when introducing CAR genes, but instead uses inexpensive vectors with naturally-derived enzymes. In addition, it does not require special facilities to contain the virus inside production suites and the need for quality testing process such as vector-derived virus checks can also be avoided. Thus, the newly developed manufacturing method is expected to reduce manufacturing costs for CAR-T cells.

J-TEC has manufacturing facilities that meet the standards⁸ for manufacturing and quality control of regenerative medical products. It develops, manufactures, and markets autologous cultured epidermis, Japan’s first regenerative medical product. The company signed the three-party patent license agreement to grow its pipeline of regenerative medical products. Tapping into its technology and knowhow on autologous cell culture, its established quality assurance system, and advanced manufacturing facilities, the company intends to promote the development of therapies using autologous CAR-T cells targeting CD 19-positive ALL.

Nagoya University began clinical research on intractable/recurrent CD 19-positive ALL with the support of the

Japan Agency for Medical Research and Development (AMED)^{*9} in February 2018. It is one of Japan's leading medical facilities for the treatment and research and development of pediatric cancer. Utilizing the knowhow cultivated in clinical practice, it will continue to promote further clinical applications.



“We had been exploring companies to partner with in clinical trials and commercialization after clinical research even before we began our clinical research in February 2018” said Professor Yoshiyuki Takahashi, Department of Pediatrics of Nagoya University, one of the inventors of the patented technology, “We chose J-TEC as our partner for its track record in the development, manufacturing, and marketing of regenerative medical products, its extensive knowhow on commercialization, and its well-equipped manufacturing and quality control facilities. In addition, Nagoya University and J-TEC are both based in Aichi Prefecture. We will work closely with J-TEC to deliver ground-breaking therapies to patients suffering from blood cancers as soon as possible.”

“This CAR-T cell manufacturing technology developed jointly by Nagoya University and Shinshu University is an extremely ground-breaking technology that does not use viruses.” said Ken-ichiro Hata, President of J-TEC. “Efforts to identify clinical applications of therapies using this technology are underway at Nagoya University, which is one of Japan’s leading sites for the treatment of pediatric cancer. It has a high affinity with our business as it also uses the patient’s own cells. By combining with our resources, such as development knowhow on regenerative medical products and our existing facilities, as well as the various technologies of the Fujifilm Group, we are confident that we will be able to accelerate the commercialization of this technology. We will work to ensure the early availability of therapies using high quality ‘autologous CAR-T cells.’”

Nagoya University will promote the development of ground-breaking therapeutic technologies including high quality cancer immunotherapy, contributing to the resolution of unmet medical needs.

J-TEC will accelerate the research and development of new regenerative medical products, contributing to the enhancement of the quality of life of patients through the commercialization and industrialization of regenerative medicine.

* 1 Patient-derived cells.

* 2 A type of transmembrane protein expressed on the surface of cells. It is particularly expressed in the early stages of antibody-producing B cell development.

* 3 A disease that develops when lymphocytes, a type of white blood cell, become malignant, and proliferate indefinitely. The disease does develop in adults, but occurs relatively frequently in children age 6 and under. This agreement targets acute lymphoblastic leukemia with the expression of CD 19 antigen.

* 4 Shared Nagoya University/Shinshu University Patent Application

Patent Application Number	PCT/JP2016/079989 (patent pending)
Name	Method of preparing genetically modified T cells with the expression of chimeric antigen receptors
Applicant	Nagoya University, Shinshu University
Inventors	Nagoya University: Nobuhiro Nishio, Yoshiyuki Takahashi Shinshu University: Yoza Nakazawa, Miyuki Tanaka, Daisuke Morita

Fiscal 2015 Japan Agency for Medical Research and Development "Project for Commercialization of Innovative Research on Cancer Therapeutics" "Development of chimeric antigen receptor T cell therapy using non-viral vectors for pediatric acute lymphoblastic leukemia" commissioned research and development, patent application filed for the application of Article 19 of the Industrial Technology Enhancement Act.

- * 5 A type of lymphocyte. Includes killer T cells that kill cells infected by viruses or bacteria, and helper T cells that activate B cells to produce antibodies and activate phagocytes that destroy pathogens, such as viruses. T cells have T cell receptors that bind specifically to certain antigens, and this is how they express an immune response to that antigen.
- * 6 Vectors are molecules that have the ability to introduce genes into cells. Viral vectors are vectors that use the nature of viruses to invade cell nuclei.
- * 7 Genes that induce T cells to express chimeric antigen receptors (CAR). CARs are proteins created by artificially modifying T cell receptors, and they recognize specific antigens that are expressed on the surface of cancer cells and have the function of inducing/activating T cells.
- * 8 Standards based on the "Law on Securing the Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices"(Enacted November 2014).
- * 9 Fiscal 2017 to 2019 Project for Commercialization of Innovative Research on Cancer Therapeutics. Subject: Commercialization of chimeric antigen receptor T cell therapy using non-viral vectors for pediatric acute lymphoblastic leukemia.

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