November 17, 2017
The University of Tokyo
BrightPath Biotherapeutics Co., Ltd.

Patent Issued in Japan on
Method for Reconstructing Immune Function Using Pluripotent Stem Cells

Tokyo, November 17, 2017— The University of Tokyo and BrightPath Biotherapeutics Co., Ltd. (TSE Mothers: 4594) announce issuance of the patent "Method for Reconstructing Immune Function Using Pluripotent Stem Cells". This method was developed in the laboratory of Professor Hiromitsu Nakauchi at the Institute of Medical Science, The University of Tokyo. Joint research for the above patent was conducted by granting an exclusive license to Advanced Immunotherapy Co., Ltd., a consolidated subsidiary of BrightPath Biotherapeutics Co., Ltd.

1. Summary of patent

Patent number:	6229958
Title of invention:	Method for Reconstructing Immune Function Using Pluripotent Stem Cells
Patent holder:	The University of Tokyo
Licensee:	Advanced Immunotherapy Co., Ltd.

2. Description of patented technology and method
This patent defines a method by which iPS cells (Note 1) are established from T cells and are then induced to differentiate into functional T cells while maintaining the recombinant structure of the TCR gene (Note 2) derived from the original T cells.

Malignant cells evade immune surveillance imposed by the patient's immune system. By replenishing or rejuvenating the function of these compromised immune cells, particularly cytotoxic T cells, one can develop an effective anti-cancer treatment regime. Of particular importance is the specific ability of these T cells to recognize cancer cells. In recent years, backed by the rapid progress of genetic engineering technology, several attempts have been made to replenish and enhance specific immune responses using *in vitro* transfection of antigen-specific TCR genes into various immune cells. However, cells developed by this method involve challenges such as low *in vitro* proliferation efficiency and functional deterioration of T cells, as well as low transfection efficiency of TCR genes.

The patent described herein defines a novel method that enables the establishment of highly proliferative iPS cells from human T cells, which can be differentiated into functional T cells. These T cells have high cytokine (Note 3) productivity while maintaining high antigen specificity via rearrangement of the same TCR gene (Note 2) as that of the original antigen-specific T cells. We strongly believe that an immune cell therapy that uses such reconstituted T cells for transplant into patients will be an effective means to improve the efficacy of cancer therapy.

[Explanation of terms]

(Note 1) iPS cells: iPS cells are pluripotent stem cells induced by transfecting certain genes (the following four genes according to initial reports: OCT3/4, SOX2, KLF4 and c-MYC) into somatic cells *in vivo*. iPS cells were reported to have been established in mice and humans in 2006 and 2007, respectively, by Professor Shinya Yamanaka of Kyoto University and his colleagues. iPS stands for induced Pluripotent Stem.

(Note 2) TCR gene / gene rearrangement: TCR stands for T cell receptor. A TCR is an antigen receptor molecule that is expressed on the cell membrane of T cells and recognizes and binds to an antigen. T cells can recognize an enormous number of antigens present on cancer cells, bacteria and viruses by forming a wide variety of TCR genes through cut-and-paste of gene segments or switching connections between them, which is called gene rearrangement.

(Note 3) Cytokine: The term cytokine refers collectively to soluble molecules that are produced by cells that induce other cells to proliferate, differentiate, activate, die or express other functions. Cytokines are produced by cells of the immune system and work on adjacent cells.

[Inquiries on this matter should be addressed to:]

Division of Stem Cell Therapy
Distinguished Professor Unit, Institute of Medical Science, University of Tokyo
TEL: +81-3-5449-5333 FAX: +81-3-5449-5451

BrightPath Biotherapeutics Co., Ltd.
Business Administration
TEL: +81-3-5840-7697 FAX: +81-3-5840-7716