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SHIBUYA CORPORATION

Development of an Automated Manufacturing System for the Industrial Scale Supply of the World First Cellular Immunotherapy Product for the Treatment of Solid Cancer

Dr. Koji Tamada, professor and chairman, Department of Immunology, Yamaguchi University Graduate School of Medicine developed a method for the proliferation of a patient's own T cells at the location of a tumor. These cells infiltrate a tumor, accumulate and survive long enough to result in profound anti-tumor effect. These chimeric antigen receptor T cells, which are called PRIME CAR-T cells have superior antitumor benefit to conventional CAR-T cells※2 and provides improved efficacy against types solid tumors for which there are no effective treatment or recurrence prevention measures currently available.

Shibuya Corporation ("Shibuya") and Noile –Immune Biotech, Inc. ("Noile")※3 founded by Dr. Tamada have entered into an agreement to jointly develop a regulatory compliant clinical grade automated manufacturing system for cancer immunotherapy cells. These systems will be targeted to serve an important emerging cancer therapy strategy, with a specific focus on CAR-T cells which are the subject of considerable oncology research.

The newly developed automated manufacturing system ("System") can manufactures PRIME CAR-T Cell at the clinical scale, and is sufficiently scalable to be developed in a suitable commercial scale post-regulatory approval. The System enables the insertion of genes into T cells collected from cancer patients to express cytokines which are able to reduce solid tumors. The resulting PRIME CAR-T cells are able to reduce solid tumors in a manner superior to conventional CAR-T cells. The System is also able to utilize automated cell culture technology to grow PRIME CAR-T cells to populations sufficient effective patient treatment. Shibuya and Noile have worked together to develop and manufacture a fully functional automated prototype working at the pre-clinical laboratory scale. A significant number of studies have been executed to prove the concept and ensure functionality. .

The System is flexible enough to be utilized for all types of cell-based immunotherapy including conventional CAR-T which are currently the subject of research and development products around the world. Shibuya will explore commercial applications of the System which can be customized to meet the specific requirements of organizations currently engaged in the research, clinical evaluation or future global commercialization of cell-based immunotherapy products.

Notes:

Cancer Immunotherapy:

Cancer Immunotherapy is a type of cancer treatment that enables a patient's immune system to fight cancer. It is made up of white blood cells as well as the organs and tissues of the lymphatic system. Immunotherapies can be used in place of or as adjuncts to current cancer treatments such as surgery, chemotherapy, and radiation therapy

***1. PRIME CAR-T Cell:**

PRIME (proliferation inducing and migration enhancing) CAR-T cell is a second generation development of CAR-T cells. PRIME CAR-T cells are engineered to express interleukin (IL)-7 and Chemokine Ligand (CCL) 19, which are factors essential to the maintenance of T-cell zones in lymphoid organs.

***2. CAR-T Cell:**

Chimeric antigen receptor T cells (CAR T cells) have gain growing scientific and public interest worldwide and are generally considered to be a breakthrough in cancer immunotherapy. CAR-T cells have shown remarkable efficacy in cancer immuno-therapy, particularly in the treatment of blood cancers but not for the treatment of solid tumors.

***3. Noile-Immune Biotech, Inc.:**

Noile-Immune Biotech is a startup collaboration between Yamaguchi University and National Cancer Center Japan and is a biotechnology company focused clinical scale research with plans to develop and commercialize the next generation CAR-T cells to eradicate solid cancers.

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Reference from a press release issued by the Japan Agency of Medical Research and Development (AMED) dated March 6, 2018

Background of Cancer Immunotherapy:

Cancer is the number one cause of death in Japan and 28.5% of total deaths reported in calendar year 2016 were the result of cancer. This death rate equates to one (1) pout of every 3.5 deaths resulting from cancer. Given the importance of cancer as a cause of morbidity and mortality in Japan, the discovery and development of effective cancer treatments, as well as the prevention of disease recurrence is both critical and urgent.

Research and development of a cancer immunotherapy has currently progressed so significantly that it is now a 4th major mode of treatment along with more conventional treatments which are surgery, chemotherapy, and radiation therapy. A particular focus of

interest are CAR-T cell therapies, which have demonstrated considerable potential. CAR (engineered receptors) to enhance a specific patient's T cell response to cancer cells have drawn considerably research interest.

An ever-increasing number of CAT-T cell therapies are in clinical researches and undergoing development around the world and particularly in Europe, US, and China. CAR-T cells have demonstrated remarkable efficacy in cancer immunotherapy, predominately in the treatment of blood cancers, such leukemia and lymphocyte tumor. However, only a small number of CAR-T cell therapies have been approved by regulatory agencies for the treatment of blood cancer. However, the use of CAR-T cell therapies against solid cancers has lagged behind. Dr. Tamada and his group conduct research and undertake development of new CAR-T cells therapies which are effective for solid tumors. The development of these new therapies, which "PRIME CAR-T cells therapy" are the result of proprietary research the basics of which are described below.

PRIME CAR-T cells, methods and Research Results

IL-7, a cytokine known to enhance the proliferation and survival of T cells and CCL19, a chemokine which increases the infiltration of dendritic cells (DC) and T cells are central features of research which has led to the development of PRIME CAR-T cells. These factors are protein substance essential for the maintenance of T cell zones in lymphoid organs. The PRIME CAR-T research has resulted in a process which utilizes the characteristics of these modified cells to enable the infiltration, accumulation and survival of T cells and DC which have been found to express anti-tumor capability against solid tumors.

Mice models to evaluate specific tumor types were created by hypodermic injections of various types of cancers. Comparative studies were done using both a conventional CAR-T cells (no IL-7 and CCL19) and PRIME CAR-T cells which were injected through a peripheral vein into mice. In this mice model, PRIME CART-T cells achieved complete regression of pre-established solid tumors and prolonged mouse survival. PRIME CAR-T demonstrated superior anti-tumor activity compared to that of conventional CAR-T cells. In addition, after 100 days, cancer cells were injected to those PRIME CAR-T cell treated mice, and this did not result in new cancer development in these mice. This indicates that PRIME CAR-T cells can create a long-term immunological memory and thereby prevent the recurrence of cancers.

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