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Healios' Gene-Edited NK Cells: Joint Research with Hiroshima University for Hepatocellular Carcinoma

HEALIOS K.K. (“Healios”) is developing next-generation cancer immunotherapies for solid tumors using NK cells*¹ derived from allogeneic iPSCs (“gene-edited NK cells”) whose specific functions have been enhanced with gene editing technology. Although solid tumors account for the vast majority of cancer deaths, there are limited treatment options for patients affected by the disease and it represents one of today’s greatest unmet medical needs. In pursuit of better outcomes for these patients, Healios is continuing with *in vitro* and animal testing of its initial NK cell therapy candidate (development code: HLCN061) to determine the range of cancers in which the product is effective and prepare for its first clinical trials.

As part of these efforts, Healios is pleased to announce that it has entered into a joint research agreement with the Department of Gastroenterological and Transplant Surgery (Prof. Hideki Ohdan), Graduate School of Biomedical and Health Sciences, Hiroshima University, to advance HLCN061 for hepatocellular carcinoma. In the initial phase of this joint research, we plan to evaluate the anti-tumor effect of HLCN061 on hepatocellular carcinoma by *in vitro* functional evaluation as well as *in vivo* evaluation in chimeric mice transplanted with normal and cancerous human hepatocytes.*²

The Department of Gastroenterological and Transplant Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, has been conducting a wide range of research from basic to clinical studies on postsurgical adjuvant immunotherapy using hematopoietic stem cell-derived activated NK cells for viral hepatitis and hepatitis associated with anti-cancer drugs, and it has also participated in past clinical research involving the use of NK cells. In particular, the department has vast knowledge and experience in the research of cancer immunotherapy for hepatocellular carcinoma.

HLCN061 has been designed to have enhanced solid cancer killing ability on a standalone basis and in combination with existing cancer drugs. The cells have demonstrated potent [anti-tumor effects in vitro and to kill cancer cells faster when used in combination with anti-cancer drugs](#). Healios has established a master cell bank of the gene-edited iPS cells used to make the NK cells and a 3D bioreactor production system, enabling it to efficiently and stably manufacture the product at scale. By conducting joint research with Hiroshima University to evaluate the anti-tumor effect of HLCN061 on hepatocellular carcinoma, Healios aims to obtain important data and advance the product to human studies as soon as possible.

Even though the advent of molecular targeted drugs and cancer immunotherapy has improved treatment outcomes for some cancer patients, the efficacy of existing treatments for solid tumors remains poor. Healios is committed to its continued research and development of effective treatments for solid cancer patients.

This action has no impact on our company’s consolidated financial results for the current fiscal year. We will promptly make the necessary announcements if any matter requiring

disclosure arises in the future.

***1 Natural killer (NK) cells**

Natural killer (NK) cells are a subset of lymphocytes, a type of white blood cell. NK cells play a central role in a cell mediated defense system that human bodies naturally have, and attack cancer cells and virus-infected cells. The expected efficacy of treatments using NK cells includes life-extension, promotion of healing, relief of symptoms, and improvement of quality of life.

***2 Chimeric mice transplanted with cancerous human hepatocytes**

Chimeric mice transplanted with human hepatocytes are mice in which at least 70% of the liver has been transplanted with human liver cells called hepatocytes. These mice express most of the genes that are expressed in a normal human liver, thus reproducing the conditions of the human liver and allowing the mice to be used in pharmacokinetic studies and research involving hepatitis viruses. In this joint research, we plan to transplant both normal and cancerous human hepatocytes into mice to produce chimeric mice with cancerous human hepatocytes for the purpose of investigating the anti-tumor effect of Healios' gene-edited NK cells.

About The Department of Gastroenterological and Transplant Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University

The Hiroshima University Department of Gastroenterology and Transplantation Surgery discovered that TRAIL, a potent anticancer molecule, can be induced in NK cells at a specific stage of maturation located in the liver, and that hepatocellular carcinoma can induce NK cell-mediated cell death by highly expressing TRAIL receptors (*Hepatology* 2006, *J Clin Invest* 2009). NK cell biology studies were conducted at Hiroshima University and the University of Miami, as published in "Immunostimulatory Therapy Using Activated NK Cells Derived from Donor Liver for the Prevention of Recurrence of Hepatocellular Carcinoma after Liver Transplantation (Type 1 Regenerative Medicine Technology)", and safety and volume-dependent improvements in survival were reported (*Cancer Immunology, Immunotherapy* 2021). In addition, the Department of Gastroenterology and Metabolism, a free-standing research center at Hiroshima University, is conducting research to develop new treatments using chimeric mouse models of human hepatocytes, which is the only technology of its kind in the world. (<https://shounai.hiroshima-u.ac.jp/liverproject/> for more information)

About Healios:

Healios is Japan's leading clinical stage biotechnology company harnessing the potential of stem cells for regenerative medicine. It aims to offer new therapies for patients suffering from diseases without effective treatment options. Healios is a pioneer in the development of regenerative medicines in Japan, where it has established a proprietary, gene-edited "universal donor" induced pluripotent stem cell (iPSC) line to develop next generation regenerative treatments in immuno-oncology, ophthalmology, liver diseases, and other areas of severe unmet medical need. Healios' lead iPSC-derived cell therapy candidate, HLCN061, is a next generation NK cell treatment for solid tumors that has been functionally enhanced through gene-editing. Its near-term pipeline includes the somatic stem cell product HLCM051, which is currently being evaluated in Japan in Phase 2/3 and Phase 2 trials in ischemic stroke and acute respiratory distress syndrome (ARDS), respectively. Healios was established in 2011 and has been listed on the Tokyo Stock Exchange since 2015 (TSE Mothers: 4593). <https://www.healios.co.jp/en> .