

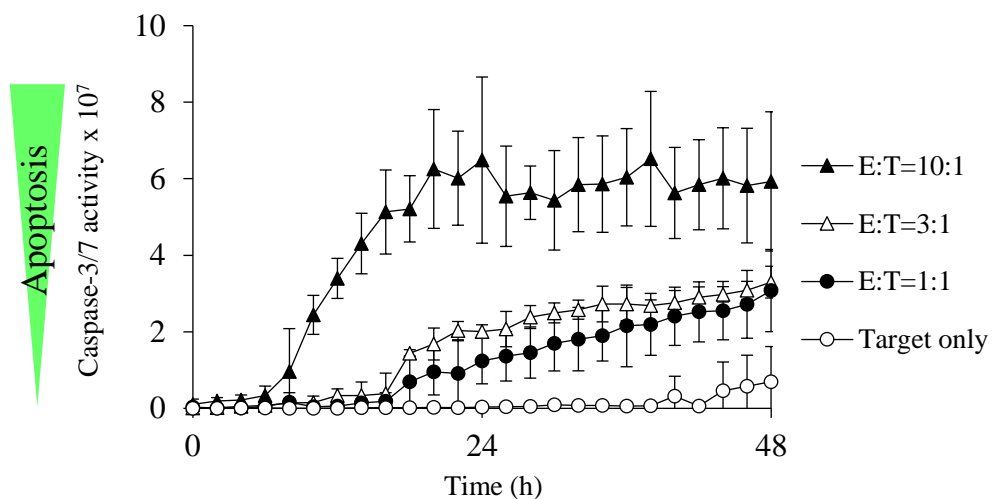
Company Name: HEALIOS K.K.
 Representative: Hardy TS Kagimoto, Chairman & CEO
 (TSE Growth Code: 4593)

Healios' eNK Cells demonstrate anti-tumor effect in lung cancer patient-derived cancer organoids

HEALIOS K.K. (“Healios”) is developing next-generation immuno-oncology therapies, with a focus on solid tumors, using NK cells^{*1} derived from allogeneic iPSCs and whose specific functions have been enhanced with gene editing technology (development code: HLCN061 “eNK cells”). Healios is pleased to announce that eNK cells have demonstrated a robust anti-tumor effect in lung cancer patient-derived tumor organoids (Fukushima Patient Derived Tumor Organoid^{*2}: “F-PDO[®]”).

The F-PDO used in this examination is a cell mass consisting of multiple cell types derived from patient tumor tissue. Histological and genetic analysis have confirmed that they maintain the properties of patient cancer tissue. Due to their similarity to the original cancer, the results of the effect of anti-tumor drugs in models utilizing F-PDO can be evaluated as more reflective of the clinical situation.

Anti-tumor effect of eNK cells in lung cancer-derived F-PDO



In this experiment, eNK cells (denoted as “E” or Effector) were added at one, three, and ten-fold ratios to the number of cells composing F-PDO (denoted as “T” or Target).

Cytotoxic activity was confirmed by measuring the induction of apoptosis (cell death) of the cancer cells.

Under conditions with added eNK cells, F-PDO cancer cell apoptosis induction could be observed after 8 hours with an E:T of 10:1, and after 18 hours with an E:T of 3:1 or 1:1. Under F-PDO only conditions without added eNK cells, apoptosis induction was not observed until around 48 hours. Healios examined several F-PDOs and generally obtained similar results (the above graph provides data for one example).

[As we disclosed in November 2021](#), Healios confirmed a robust in vitro anti-tumor effect of eNK cells in a lung cancer cell line (A549, non-small cell lung carcinoma). Healios also demonstrated that eNK cells have anti-tumor effects in mice engrafted with human lung cancer cells and human liver cancer cells, thereby establishing “animal proof-of-concept” for the efficacy of eNK cells (please see [page 32-34 Business Briefing Session Presentation Slides in 2022](#)). The results of this examination using F-PDOs further indicate the promise of eNK cells as an effective therapy for patients with solid tumors.

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.

***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 Organoids**

Organoids are tissues with three-dimensional structures that have characteristics quite similar to those of tissues and organs in living organisms.

*This examination was commissioned by Healios to the Fukushima Translational Research Foundation and conducted at FUJIFILM Wako Bio Solutions Corporation.

About Healios’ eNK cells:

Healios’ eNK cells are an iPSC-derived NK cell therapy with several functional enhancements achieved through gene-editing including enhanced recognition of and cytotoxicity towards cancer, improved persistence, increased capability to migrate to and infiltrate solid tumors, and the ability to recruit host immune cells. Healios has succeeded in developing eNK cells through its own research and has confirmed the anti-tumor effect of

eNK cells in mice engrafted with human lung cancer cells and human liver cancer cells. In joint research with [the National Cancer Center Japan](#) (“the NCCJ”) Healios is evaluating the antitumor effect of eNK cells in a PDX mouse disease model created using the NCCJ’s JPDX samples. Healios is also conducting joint research using eNK cells for hepatocellular carcinoma with [Hiroshima University](#) and for mesothelioma with [Hyogo Medical University](#). Healios is continuing with in vitro and in vivo testing of its eNK cell therapy in preparation for its first clinical trials. In addition to advancing eNK cells as a monotherapy and in combination with existing drugs, Healios is developing a dual CAR-eNK cell product, in which chimeric antigen receptors (CARs) that specifically recognize cancer antigens are introduced into the eNK to facilitate enhanced targeting of certain solid cancers.

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 has been 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 Growth: 4593).

<https://www.healios.co.jp/en>

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