

July 3, 2024

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

**Academic paper on Helios UDC in "Stem Cell Research and Therapy"
Hypoimmunogenic human iPSCs expressing HLA-G, PD-L1, and PD-L2
evade innate and adaptive immunity**

HEALIOS K.K. (“Healios”) is involved in the research of new therapeutic products using Universal Donor Cells (“UDCs”)*, which are next-generation iPSC cells created with gene-editing technology that have a reduced risk of immune rejection regardless of a patient’s HLA type. We are pleased to announce that researchers at Healios have published a recent work revealing that hypoimmunogenic human iPSCs, which have diminished the expression of polymorphic HLA molecules and forced the expression of HLA-G, PD-L1, and PD-L2, can evade both innate and adaptive immunity. This work has been published in the peer-reviewed journal "[Stem Cell Research & Therapy](#)".

Title: [Hypoimmunogenic human iPSCs expressing HLA-G, PD-L1, and PD-L2 evade innate and adaptive immunity](#)

Journal: [Stem Cell Research & Therapy](#)

DOI: 10.1186/s13287-024-03810-4

Authors: Norihiro Tsuneyoshi#1, Tomonori Hosoya#1, Yuriko Takeno#1, Kodai Saitoh, Hidetaka Murai, Naoki Amimoto, Rie Tatsumi, Sono Watanabe, Yudai Hasegawa, Eri Kikkawa, Kumiko Goto, Fusako Nishigaki, Kouichi Tamura*, and Hironobu Kimura*

#1: These authors have equally contributed.

*Corresponding author

Tsuneyoshi et al. have shown that Healios UDCs do not have chromosomal abnormalities and can differentiate into the three-germ layers, including hematopoietic progenitor cells, hepatocytes, and vascular endothelial cells. They also demonstrated that these cells acquire tolerance to innate and adaptive immunity and that the integrated suicide gene functions as a safety switch. This work indicates that Healios UDCs have sufficient potential as a source of regenerative medicine products for transplantation.

Healios is a pioneer in the development of regenerative medicines and is advancing efforts to create new therapeutic medicines using iPSC and other cell lines. Over its greater than a decade of developing iPSC products, Healios has built a suite of proprietary technologies that includes high quality, clinical grade iPSC cell lines. In 2020, Healios completed the generation of a clinical-grade UDC iPSC line as a next-generation technology platform for the creation of regenerative medicine products with enhanced efficacy and safety by suppressing immune rejection, while maintaining the inherent characteristics of iPSCs such as unlimited self-renewal and pluripotency to differentiate into various cells (Please see "[Successful Establishment of Healios’ Proprietary Clinical Grade Universal Donor iPSC Cell Line](#)" released on October 20, 2020). Since then, Healios has provided UDCs to research institutes and

companies around the world as a promising raw material for cellular medicines and verified their potential in relation to a wide range of diseases.

We will continue our research into the clinical application of UDC and promote research and development of innovative regenerative medicine technologies for patients suffering from diseases with high unmet medical needs. We also aim to make significant progress in the world of regenerative medicine through joint research and out-licensing of our UDC as a de facto standard product.

*** UDC**

UDCs are iPS cells created using gene-editing technology that allows them to avoid and / or reduce the body's immune rejection response. The production of Healios' UDCs involve the removal of certain HLA genes that elicit a rejection response and the introduction of certain genes to improve immune evasion and safety in an allogeneic iPS cell. This next-generation technology platform allows for the creation of regenerative medicine products with enhanced safety and a lower risk of immune rejection, while preserving the inherent ability of iPS cells to replicate themselves continuously and their pluripotency in differentiating into various other kinds of cells.

About Healios:

HEALIOS K.K. 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 and owns proprietary, global platforms utilizing both somatic stem cells and iPS cells. In the somatic stem cell field, Healios is developing MultiStem® (HLCM051), a proprietary cell product comprised of multipotent adult progenitor cells ("MAPCs") derived from the bone marrow of healthy adult donors. MultiStem has been shown to exhibit powerful anti-inflammatory and immunomodulatory properties with applicability in a range of disease states, has been tested in hundreds of patients in late stage clinical trials, is manufactured consistently at scale in 3D bioreactors, and has demonstrated both safety and suggested efficacy in hundreds of patients across multiple indications. Healios is seeking to advance MultiStem on a global basis for ischemic stroke, ARDS, and trauma. In the iPSC regenerative medicine field, Healios' lead candidate, HLCN061, is a next generation NK cell treatment for solid tumors that has been functionally enhanced through gene-editing. These cells have demonstrated robust anti-tumor efficacy in animal models, benefit from a scalable 3D bioreactor manufacturing process, and are currently being prepared for initial human testing. The company has also established a proprietary, gene-edited "universal donor cell" induced pluripotent stem cell line to develop next generation regenerative treatments in immuno-oncology, ophthalmology, liver diseases, and other areas of severe unmet medical need. 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>

Contact:
IR & Finance and Accounting Division
HEALIOS K.K.
E-mail: ir@healios.jp