

FOR IMMEDIATE RELEASE

Heartseed Enters into induced Pluripotent Stem Cell Purification Patent License Agreement for Commercialization of Cell Therapy

Aiming at contributing to the industrialization of iPSC-based therapies in areas other than the heart by out-licensing our proprietary platform technology "Metabolic Selection"

TOKYO, JAPAN, September 5, 2023 – Heartseed Inc. (CEO: Keiichi Fukuda; hereinafter referred to as "Heartseed") today announced that it has entered into a worldwide non-exclusive patent license agreement (hereinafter referred to as the "Agreement") with a biotech company (hereinafter referred to as the "Licensee") regarding a part of our proprietary purification platform, the Metabolic Selection technology.

Background and Contents of the Agreement

As the clinical application of cell therapies using induced pluripotent stem (iPS) cells progresses, there is a growing demand for the removal of undifferentiated iPSCs that may cause tumor formation.

The technology covered by this Agreement aims to selectively remove undifferentiated iPS cells by inhibiting the fatty acid synthase that is highly expressed in those cells.

Covered Patent: Patent No. JP6811489(B) and foreign patent applications*¹

The Licensee, which specializes in manufacturing mesenchymal stem cells from iPSCs for various diseases, aims to enhance regenerative medicine development by efficiently eliminating undifferentiated iPSCs using Heartseed's technology.

Under the terms of the Agreement, Heartseed grants the Licensee a non-exclusive license with the right to sublicense. Heartseed receives an upfront payment and is eligible to receive royalties on the Licensee's net sales of covered products. The name of the Licensee, financial terms, and other details remain undisclosed.

Heartseed's Metabolic Selection

Heartseed aims to commercialize cardiac regenerative medicine by producing highly purified cardiomyocytes from iPS cells and forming microtissues called cardiac spheroids for transplantation into the patient's heart. In collaboration with the Division of Cardiology at Keio University School of Medicine, Heartseed has developed "Metabolic Selection" technologies that efficiently removes undifferentiated iPS cells and non-cardiomyocytes by focusing on the differences in energy metabolism among cell types and by optimizing the composition of the culture medium. Metabolic Selection technologies, which have been published in top-tier academic journals by Dr. Shugo Tohyama et al., Division of Cardiology at Keio University School of Medicine, include the fatty acid synthesis inhibition method, as well as the lactate

method and the glutamine method, which are widely known to efficiently and selectively obtain cardiomyocytes.

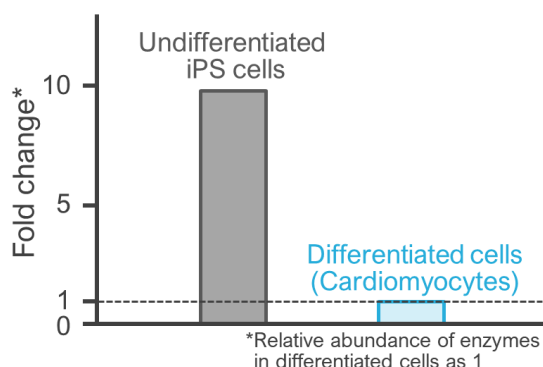
- Lactate method : Tohyama S, et al., Cell Stem Cell. 2013: 12:127-37
- Glutamine method : Tohyama S, et al., Cell Metabolism. 2016: 23:663-674
- Fatty acid synthesis inhibition method : Tanosaki S, Tohyama S, et al., iScience. 2020: 23:101535
Tanosaki S et al., STAR Protocols. 2022: 3: 101360

Fatty Acid Synthesis Inhibition Method of the Agreement

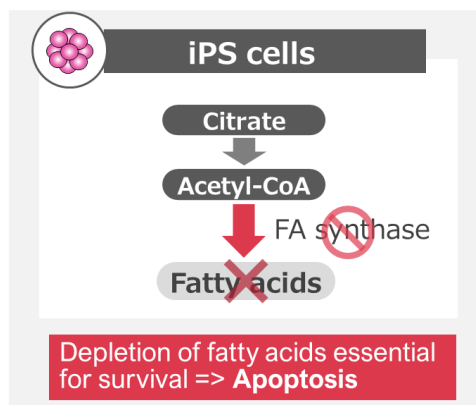
The fatty acid synthesis inhibition method covered by the agreement is a technology that enables the removal of undifferentiated iPS cells with a view to clinical application through an extremely simple process that is suitable for large-scale manufacturing for industrialization.

It is known that the expression of fatty acid (FA) synthase is about 10 times higher in undifferentiated iPS cells than in differentiated cardiomyocytes. Therefore, inhibiting fatty acid synthase with a chemical compound selectively blocks the synthesis of essential fatty acids required for undifferentiated iPS cells, leading to cell death (see the figure below).

Differences in FA synthase expression



Effects of FA synthase inhibition



based on Tanosaki S, et al., iScience. 2020.

On the other hand, the effect on differentiated cardiomyocytes is limited, and cell death is not observed. Furthermore, the fatty acid synthesis inhibition method has the potential to be utilized for the removal of undifferentiated iPS cells in other cell types, such as neurons and liver cells. Heartseed intends to further promote licensing to companies interested in utilizing our patents related to Metabolic Selection in areas beyond cardiac regenerative medicine, thereby contributing to the practical application of cell therapy using iPS cells.

Comment from Keiichi Fukuda, Founder and CEO of Heartseed

"We are delighted to have concluded this license agreement for our proprietary purification technology. One of the hurdles in the practical application of cell therapy derived from iPS cells is the concern over the presence of undifferentiated cells, which poses safety risks. The technology covered by this agreement is applicable to various differentiated cell types and is designed for the industrialization of cell manufacturing, as well as our existing Metabolic Selection methods. We intend to expand licensing of this

technology to those who need it and contribute to the industrial application of iPSC-based therapies."

*1 Heartseed has obtained the exclusive license from Keio University

About Heartseed

Heartseed Inc. was founded in 2015 to develop and commercialize cardiac remuscularization therapy developed by Professor Keiichi Fukuda and his group at the Department of Cardiology, Keio University, Tokyo, Japan. Heartseed has proprietary technologies throughout the entire manufacturing process of the cardiomyocyte-cell product, including purification, cell delivery and iPSC production.

Heartseed announced the global collaboration and license agreement with Novo Nordisk A/S for HS-001 in June 2021. Heartseed received "Minister of Science and Technology Policy Award" at Japan Venture Awards 2021 and "Ministry of Education, Culture, Sports, Science and Technology Award" at Academic Startups 2021, and "Most Promising Pipelines Awards (iPSC)" at Asia Pacific Cell & Gene Therapy Excellence Awards 2022, and "Grand Prix" at 4th IP BASE AWARD 2023. For more information, visit heartseed.jp, [LinkedIn](#) and [YouTube](#).

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