



PRESS RELEASE

March 10, 2020

Heartseed Inc.
MEDIPAL HOLDINGS CORPORATION
SPLine Corporation

Notice of Capital and Business Alliance between Heartseed and MEDIPAL HOLDINGS -Cooperation in Product Development for Innovative Cardiac Regenerative Medicine-

Tokyo-based Heartseed Inc. (“Heartseed”), a Keio University-originated biotechnology company developing induced pluripotent stem cell (iPSC)-derived cardiac regenerative medicine, and MEDIPAL HOLDINGS CORPORATION (“MEDIPAL”) today announced that they have entered into a capital and business alliance.

In conjunction with the alliance, MEDIPAL will acquire an equity stake in Heartseed. In addition, MEDIPAL and its wholly owned subsidiary SPLine Corporation (“SPLine”) will begin collaborative research with Heartseed on the logistics of Heartseed’s clinical trial supplies.

Purpose of the Alliance

Heartseed is developing HS-001, allogeneic iPSC-derived cardiomyocyte spheroids for severe heart failure, which currently has no effective treatment other than heart transplantation. In preparation for the initiation of its clinical trial, Heartseed will outsource its manufacturing to Nikon CeLL innovation Co., Ltd., and are discussing transport of the cardiomyocyte spheroids with MEDIPAL.

MEDIPAL has established a distribution system in compliance with Japanese Good Distribution Practice (GDP) guidelines. MEDIPAL is a pioneer in logistics services in the growing field of regenerative medicine, and has an extensive track record to support development of regenerative medicine products and to build a logistics system for them using its ultra-low temperature transport system.

In this alliance, MEDIPAL will contribute to the improvement of patient care by promoting development of Heartseed’s innovative products from the clinical trial stage with its experience and expertise in the distribution of regenerative medicine products.

Comment from Heartseed CEO Keiichi Fukuda, MD, PhD, FACC

“The iPSC-derived cardiomyocyte spheroids we are developing are unique in the mechanism that cardiomyocytes are strengthened by turning them into microtissues. The spheroids will be retained and engrafted with the ventricular myocardium for a long-term and are expected to contribute sustained direct ventricular contraction (remuscularization). It is completely

different from conventional treatment methods. To deliver the treatment to patients, logistical considerations are also important, and we are pleased to partner with MEDIPAL, which has an extensive track record in distribution of cellular medicines.”

Comment from MEDIPAL Representative Director, President and CEO Shuichi Watanabe

“Their investigational agent has the potential to be an innovative treatment option for patients with severe heart failure. Promoting the development and stable supply of specialty pharmaceuticals is our mission, based on MEDIPAL’s management philosophy of ‘contributing to people’s health and the advancement of society through the creation of value in distribution.’ In this alliance, SPLine, which performs logistical planning for specialty pharmaceuticals, will be involved from the clinical trial stage, and will also work with us in creating a distribution system to ensure safe and reliable delivery of the product to patients after its launch.”

Development of HS-001

Heartseed has allogeneic iPSC-derived highly purified ventricular-specific cardiomyocyte spheroids (HS-001) as its lead pipeline candidate, and is conducting research and development for the early commercialization of cardiac regenerative medicine using iPSCs supplied by the Center for iPS Cell Research and Application (CiRA) at Kyoto University. HS-001 is produced by differentiating into ventricular-specific cardiomyocytes from iPSCs with the most frequent human leukocyte antigen (HLA) type¹ in Japanese people, and removing undifferentiated iPSCs and non-cardiomyocytes to achieve high purity. To improve the engraftment rate, these cardiomyocytes are formed into spheroids in which approximately 1,000 cardiomyocytes are aggregated.

Since 2016, Heartseed has had more than 10 meetings with the Pharmaceuticals and Medical Devices Agency (PMDA), with discussions mainly focused on details of nonclinical safety studies, manufacturing processes, and quality management that are required for initiating clinical trials. Heartseed is currently conducting the nonclinical safety studies under Good Laboratory Practice (GLP)² standards under the agreement of the PMDA on their designs.

Prior to the company-sponsored clinical trials, investigator-initiated clinical trial plan of HS-001 at Keio University had been under review by the Keio University Certified Special Committee for Regenerative Medicine since May 2019 and was approved in February 2020. This plan will be submitted to the Health Science Council of Ministry of Health, Labor and Welfare after going through established procedures in Keio University Hospital. For 90 days from its submission to the Council, the plan will be examined for conformance with the regenerative medicine provision standards. If conformance is verified, Keio University will be notified and may then begin clinical research.

1. HLA type: White blood cell type, immune rejection is less likely when the HLA type matches.
2. GLP(Good Laboratory Practice): Standards for conducting studies to assess drug safety. These standards should be followed when conducting safety studies using animals in the preclinical stage.

Summary of HS-001

Generic name	Human (allogeneic) iPSC-derived highly purified ventricular-specific cardiomyocyte spheroids
Target indication	Severe heart failure, particularly heart failure with reduced ejection fraction
Route of administration	Transplantation into the left ventricular myocardium of patients with severe heart failure, using a specially designed injection device developed to minimize bleeding and enable safe and efficient transplantation of large numbers of cardiomyocyte spheroids.
Expected mode of action	The transplanted cardiomyocytes produce cytokines that have a restorative effect on cardiac function and promote neovascularization. In addition, the cardiomyocytes electrically couple with the patient's heart and remain engrafted for a long time to generate contraction of cardiac muscle. HS-001 is expected to be the world's first true regenerative medicine to contribute to long-term improvement of cardiac function in patients with severe heart failure.

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About Heartseed Inc.

Name: Heartseed Inc.
Established: November 2015
Business: Cardiac regenerative medicine using iPSCs
Shareholders: Founders/employees, Angel Bridge, Astellas Venture Management LLC, Shibuya Corporation, SBI Investment Co., Ltd., JMDC Inc., Gene Techno Science Co., Ltd., Nissay Capital Co., Ltd., SMBC Venture Capital Co., Ltd.
Head office: Shinjuku-ku, Tokyo
Website: <http://heartseed.jp/en>
Representative: Keiichi Fukuda, MD, PhD, FACC, Founder and CEO

About MEDIPAL HOLDINGS CORPORATION

Name: MEDIPAL HOLDINGS CORPORATION
Established: May 1923
Business: As a holding company, MEDIPAL controls, administers and supports the operating activities of companies in which it holds shares in the Prescription Pharmaceutical Wholesale Business; the Cosmetics, Daily Necessities and OTC Pharmaceutical Wholesale Business; and the Animal Health Products and Food Processing Raw Materials Wholesale Business, and conducts business development for the MEDIPAL Group.
Head office: Chuo-ku, Tokyo
Website: <https://medipal.co.jp/english>
Representative: Shuichi Watanabe, Representative Director, President and CEO

About SPLine Corporation

Name: SPLine Corporation
Established: May 2016
Business: SPLine proposes specialty pharmaceutical distribution plans, connects pharmaceutical manufacturers with operating companies in the MEDIPAL Group, and plans distribution systems tailored to the characteristics of each specialty pharmaceutical product. Using various bases, including the ALCs³ and FLCs⁴ – the MEDIPAL Group’s highly functional distribution centers – SPLine reliably and uniformly provides high-quality services throughout Japan based on strict quality control, delivering pharmaceutical products to medical institutions through a safe and secure distribution network.
Head office: Chuo-ku, Tokyo
Website: <http://sp-line.co.jp/en>
Representative: Atsushi Takumiya, Representative Director, President and CEO

3.ALC: Area Logistics Center

4. FLC: Front Logistics Center

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