

Eat Well, Live Well.



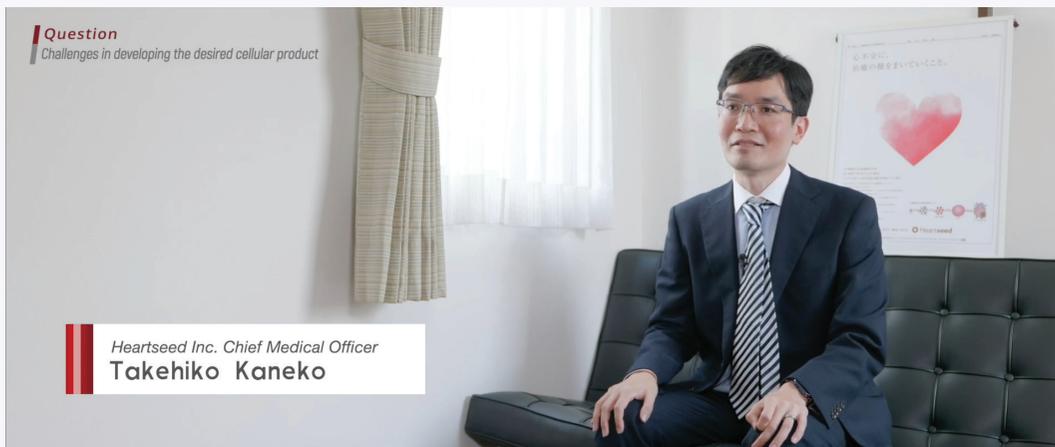
Supporting Scientists & the Future of Healthcare

Ask the Experts Series



Ajinomoto Co., Inc. (Ajinomoto) is proud to support Heartseed with high quality StemFit™ media for the differentiation and purification of their lead pipeline, HS-001. HS-001 is an investigational cell therapy using purified cardiomyocytes derived from induced pluripotent stem cells (iPSC) and currently under development by Heartseed for the treatment of advanced heart failure.

This article is a transcript of an interview conducted by Ajinomoto with Takehiko Kaneko and Keiichi Fukuda at Heartseed. The original interview movie is available from the following link. [Ajinomoto StemFit™ Supporting Scientists & the Future of Healthcare\(Full Ver.\)](#)

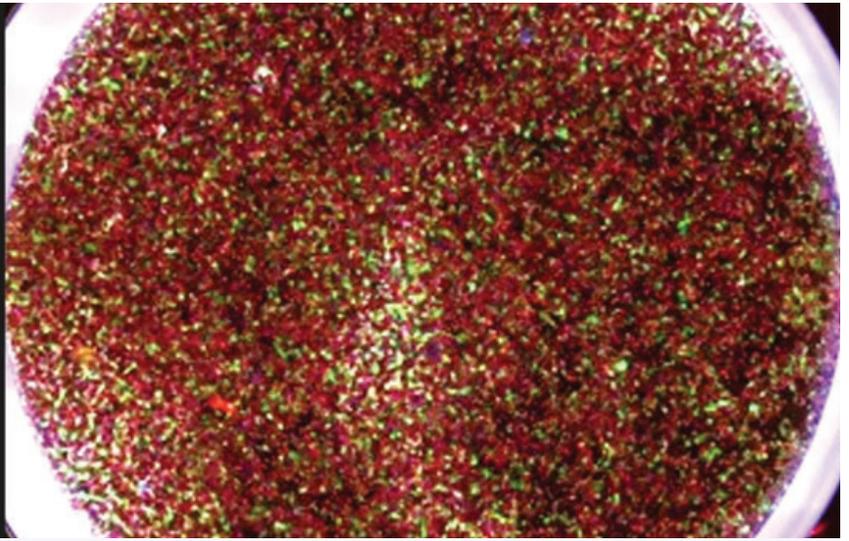


| Interview with Takehiko Kaneko (Heartseed Inc. Chief Medical Officer)

- **CHALLENGES IN DEVELOPING THE DESIRED CELLULAR PRODUCT**

Eliminating of the residual iPSCs are critical to prevent the teratoma formation. [Because] teratoma formation and is a high hurdle to create iPSC therapy products, especially our MOA (mechanism of action) is risked by remuscularization. [The] cell needs to stay in ventricular wall and stay for a long time so undifferentiated cell might cause teratoma formation. So elimination is quite important. Ajinomoto provided the sample media for many times. Dr. Fukuda's lab tried and tested media, and gave feedback to Ajinomoto. Ajinomoto provided the media many times, and thanks to Ajinomoto's contribution, we finally developed differentiation and purification protocol. Thanks to Ajinomoto's great support, Heartseed can optimize the protocol of differentiation and purification of cardiomyocytes. Heartseed can reproducibly manufacture cardiomyocyte products.

Early-stage Culture



| CLINICAL TRIAL CONSULTATIONS WITH PMDA (PHARMACEUTICALS AND MEDICAL DEVICES AGENCY)

Our mechanism of action is remuscularization, which no precedents exist. In that situation, we have to develop our way by ourselves. We had many discussions with PMDA before the clinical trial notification submission. There are three key success factors to achieve a speedy approval of the clinical trial notification. First, our pre-clinical data is very clear in safety and efficacy. So based on the very clean data, we discussed PMDA rapidly and get very positive feedback on clinical notification. Secondly, PMDA reviewed all raw materials of our product. Of course, including the media was a key discussion point. Ajinomoto provided support to answer the questions of PMDA. Thanks to Ajinomoto's great contribution, PMDA agreed [to] our manufacturing process and start review of clinical trial notification. Finally, our research collaborator Keio University have deep insight of the cardiomyocyte manufacturing, and they supported us to provide answers to the PMDA's questions.

- **EXPECTATIONS FOR AJINOMOTO**

Obviously, culture medium is very important for manufacturing of iPSC derived product. To reach out to the worldwide market, we need to manufacture more and more amount of iPSC derived products. In that situation, quality assurance and cost reduction of media is the key critical factor. I appreciate cross collaboration across Ajinomoto's departments in charge of business development, manufacturing, and R&D. I hope that Ajinomoto will continuously play a vital role of manufacturing the media.

- **HEARTSEED AND AJINOMOTO COLLABORATION**

I started myocardial regeneration research using stem cells in 1995. Initially, we demonstrated that cardiomyocytes can be regenerated using bone marrow stem cells. Since a large amount of



Interview with Keiichi Fukuda (Heartseed Inc. CEO/MD Ph.D.)

cardiomyocytes are required to treat heart disease, we have shifted our research to human ES cells and iPS cells. Research has progressed, and human cardiomyocytes can be obtained from these cells. However, it has become clear that the residual undifferentiated iPS cells and the mixture of non-cardiomyocytes are problems for the clinical use of myocardial cells produced from iPS cells.

In the process of purifying cardiomyocytes, we found that cardiomyocytes and iPS cells have different energy-metabolizing enzymes and required different nutrients for the cell survival. Therefore, I came up with the idea of purifying cardiomyocytes using the ingenious composition of the cell culture medium. When I reported it at an academic conference, a researcher of Ajinomoto, Mr. Okamoto listened to my talk and had a discussion after the lecture. From that time, our collaboration between Keio University and Ajinomoto had started.

By putting various ideas into the production of culture medium, I found that there were endless possibilities of cell culture methods, so I decided to proceed by research together with Ajinomoto. After that, I funded academia-based bio-venture, Heartseed, in 2015 because of the prospect that myocardial regenerative therapy will be realized, and I am currently conducting clinical trials. We believe that Ajinomoto is an important partner in its development.

- **ADVANTAGES OF WORKING WITH AJINOMOTO**

I thought that each composition of the culture medium has a special meaning, and that there was an optimum concentration according to its



purpose. For this reason, I planned to jointly develop a cell culture medium with Ajinomoto. One of the great things about Ajinomoto is that it has a high ability to analyze the composition of the cell culture medium. For example, regarding how the components of the cell culture medium changed before and after cell culture, the latest science such as mass spectrometry is used to analyze how each component changed. This was extremely effective in finding the optimal conditions for cell culture.

Secondly, according to our requirements, we asked Ajinomoto to adjust each component of the culture medium and to engage in a huge amount of experiments to determine the optimum concentration of each component, and experimental media with various compositions. This made it possible to produce a culture medium with favorable conditions that cannot be achieved with existing media.



As a result, we were able to obtain three culture media: iPS cell amplification medium, cardiomyocyte differentiation induction medium, and cardiomyocyte purification medium. I think that Ajinomoto's high level of science and the breadth of the bosom [generosity of heart] that did not rush the results were great.

- **EXPECTATIONS FOR AJINOMOTO**

Regenerative medicine is expected to become an important medical treatment in the 21st century. To date, most of the researchers and companies purchased the common existing cell culture medium. However, in the future, each cultured cell will have optimal culture conditions, so it will be necessary to use the best culture medium for each cell. Ajinomoto has the ability to analyze the composition of culture medium and the metabolic pathway of each cell in detail. By fully utilizing this power and supplying the culture medium to this new industrial area, we hope that Ajinomoto will grow up into a company that will play a great role as a leader of the next generation.

- **FUTURE PROSPECTS OF HEARTSEED**

Heartseed is currently conducting a clinical trial of human iPSC-derived regenerated cardiomyocyte transplantation into the patients with heart failure caused by ischemic heart disease. If we can show the safety and efficacy in this clinical trial, we can obtain the manufacturing approval in Japan. In addition to myocardial regenerative medicine, we would like to develop regenerative medicine technology in various fields using our iPS cell technology.

| The Ajinomoto Group: Strengths for iPS Cell Culture Medium Development

Ingredient manufacturing technologies

As the world's leading supplier of high-quality amino acids, which are mainly used for pharmaceuticals, Ajinomoto Co. can supply amino acids free of animal-derived components and with full traceability.

Composition and formula design

With our heritage of research into amino acid nutrition and metabolism, Ajinomoto Co. possesses the technologies and "know-how" to quickly determine the optimal composition of the dozens of components that comprise a culture medium.

Analysis technologies

Ajinomoto Co.'s analysis technologies for amino acids and trace ingredients are highly sensitive and highly accurate. This permits us to formulate a high-performance culture medium with exacting quality control.

| StemFit™: The Perfect Fit for Stem Cell Research

Conventionally, iPS cells were cultivated in a culture medium that included mouse cells and other animal and human-derived components. StemFit™ is highly safe because the risk of accidental biological contamination is minimized. To confirm this point, Ajinomoto Co. consulted with the Pharmaceutical and Medical Devices Agency (PMDA) of the Government of Japan, which determined that StemFit™ does not contain any animal- or human-derived components after an intensive review process.

StemFit™ is a high-performance, high-quality culture medium. Cells proliferate in the StemFit™ culture medium at a high growth rate, making research not only more efficient, but also more cost effective.

Ajinomoto is committed to the advancement of regenerative medicine with StemFit™ Media and Growth Factors. Chemically defined and Animal-Origin-Free, our products enable consistent experimental results and support the development of cell therapy products.

For more information, please visit <https://www.ajitrade.com/stemfit/> and chat with us today Or contact us:

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