To our shareholders and investors,

Thank you sincerely for your ongoing support of Heartseed Inc. I am Keiichi Fukuda, CEO of the company. I would like to share with you about my invited lecture at a conference in Göttingen, Germany.

■ About the CVBE (Cardiovascular Bioengineering) Symposium

CVBE is an international conference supported by the NIH (National Institutes of Health) in the United States, and this year marked its 10th edition, held in Göttingen, Germany from June 18 to 20. The conference is organized on a rotating basis by leading scientists from around the world, and I myself hosted the 7th edition in Kyoto in 2023. This year's conference was organized by Professor Wolfram Zimmermann of the University of Göttingen — a friend and rival of mine — and brought together approximately 200 attendees at the hall of the German Primate Center (Deutsches Primatenzentrum: DPZ).

Professor Wolfram Zimmermann (left)

The conference brings together researchers working in regenerative medicine, gene therapy, tissue engineering, and other fields related to cardiovascular disease, with a particular focus on technologies that may ultimately be translated into clinical practice. I am deeply honored to have been invited on six occasions, though I note with some concern that in the two most recent editions, no other Japanese researchers were among the invited speakers — a situation I find regrettable and one that gives me pause about the future of research in Japan.

With Professor Erwin Neher (left), Nobel Laureate in Physiology or Medicine. He is known as the developer of the patch-clamp technique, which revolutionized the study of ion channels in nerve cells.

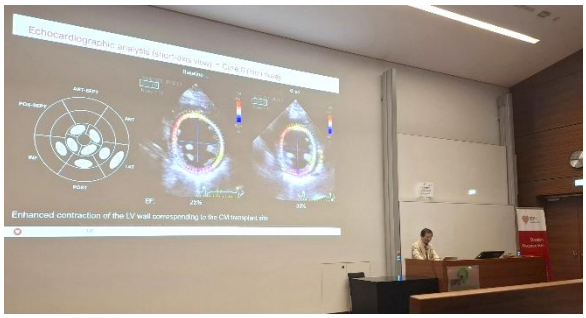
On a side note, I had the privilege of attending special lectures by two Nobel laureates at this conference. The photo on the right shows Professor Erwin Neher, who developed the patch clamp technique — the world's first method for analyzing the electrical excitability of nerve cells — and demonstrated the existence of Na channels in neurons. Being able to hear a lecture in person from, and exchange views with, a scholar whose work I have long studied through papers and textbooks was a stroke of luck I find truly difficult to put into words.

■ Regarding Presentations by Other Groups

Approximately 40 researchers presented their work at this year's conference. Among the most anticipated sessions was a series of clinical updates in the field of regenerative medicine presented on the afternoon of the second day. In addition to my presentation, researchers reported on a variety of approaches, including direct transplantation of isolated cardiomyocytes, engineered myocardial patches, extracellular vesicle-based therapies, and mesenchymal stem cell therapies. While I will refrain from discussing the details of presentations by other researchers and companies, it was clear that significant efforts are underway around the world to bring regenerative therapies for severe heart failure into clinical practice.

While each approach has its own scientific background and technical characteristics, the discussions held throughout the conference reaffirmed that establishing regenerative medicine for severe heart failure requires three essential criteria: high engraftment rates of transplanted cardiomyocytes, a strong safety profile with reduced risks such as arrhythmia, and safe and precise delivery to the targeted site. I confirmed that these represent significant hurdles for all groups in the field, and that our own technological approach to these challenges has been well-founded. This gave me renewed confidence in the competitiveness of our technology.

■ Highlights of Our Presentation



I began with a review of our company's technology, covering the following four points: 1) differentiating ventricular-specific cardiomyocytes to reduce arrhythmias; 2) achieving approximately 99% purification through our proprietary cardiomyocytes purification methods, such as the lactate acid selection method and glutamine selection method, to prevent tumor formation; 3) forming cardiomyocytes into clusters of approximately 1,000 cells — prior to transplantation in order to improve post-transplant engraftment rates; and 4) using transplantation needles designed to minimize bleeding during puncture, in consideration of patient safety.

I also presented findings from the LAPiS study, the clinical trial of HS-001. In particular, I showed that the patients ultimately enrolled in the LAPiS study were equivalent to, or more severe than, those enrolled in the STICH trial conducted in the United States. The STICH trial evaluated the impact of coronary artery bypass grafting (CABG) on survival outcomes in

patients with heart failure and a left ventricular ejection fraction of 35% or less, and demonstrated only limited improvements in ejection fraction and cardiac remodeling following surgery. Building on this, I reported that among 10 patients in total — 5 in the low-dose group (1-year follow-up) and 5 in the high-dose group (6-month follow-up) — 8 showed either "significant improvement" or "mild improvement" in measures of cardiac size, pump function, cardiac load, and indicators of physical functioning and stamina. As for the remaining 2 patients, whose clinical outcomes did not improve to the same degree as the others, I noted that there were individual explanations for each case — such as the worsening of mitral valve regurgitation that had been present prior to surgery — and that these factors had an impact on their apparent clinical results. In addition, I presented echocardiography and MRI videos from multiple cases, reporting improvements in myocardial contractility in regions unrelated to the coronary artery bypass graft area, along with the corresponding analytical findings.

As the highlight of the presentation, I reported that the first case of the EMERALD study — a clinical trial administering cardiomyocyte spheroids via catheter — had been completed successfully. I explained that the delivery catheter is equipped with a mapping system capable of identifying the precise location of the catheter tip within the left ventricle. In addition, electrodes incorporated into the catheter tip allow physicians to confirm, via ECG monitoring, when the needle has successfully penetrated the myocardial wall. These features are designed to facilitate accurate and controlled delivery of cardiomyocyte spheroids to the intended site. Furthermore, by showing videos of the actual procedure, I helped the audience understand that the operation is similar to existing catheter procedures and does not require a significant amount of time to master.

The presentation generated considerable interest among researchers, as reflected in the many thoughtful questions and discussions that followed. I was particularly encouraged by the positive feedback regarding the evolution of cardiomyocyte replacement therapy toward practical clinical application through a catheter-based delivery approach. Such feedback reinforced my confidence in the potential of this technology and strengthened my determination to bring new treatment options to patients suffering from heart failure around the world as quickly as possible.

■ In Closing

The presentation delivered at CVBE built upon the data and findings that I previously presented at the Keystone Symposia held in January of this year. I was encouraged by the strong level of interest in Heartseed’s clinical development programs. In particular, our integrated approach to achieving high cell engraftment rate, safety, and delivery technology

attracted significant attention from researchers in the field.

Regarding the final data from the LAPiS study, we are eager to share specific figures with you as soon as possible. However, in order to maximize the value of regenerative medicine products, the strict preservation of "unpublished data (novelty)" for presentation at academic conferences and in journal publications is required as a globally accepted standard. Releasing this data prematurely would risk undermining the academic credibility of the researchers who will become our future customers, as well as the long-term business value of the company, which could ultimately be to the detriment of our shareholders.

Furthermore, as we advance our dialogue with regulatory authorities toward our target of application for approval within this year, we are in an extremely sensitive period where every word carries significant weight. We hope you will view this as a preparatory phase leading up to our next major milestone — and at the same time, a period of "energy accumulation" in advance of a great leap forward.

Heartseed Inc.　President and CEO　Keiichi Fukuda

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