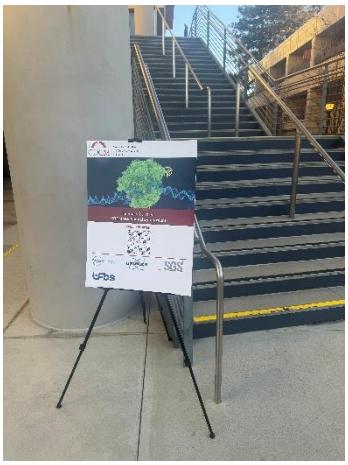
To our stakeholders,

I would like to express my sincere gratitude for your continued support of Heartseed Inc. I am Keiichi Fukuda, CEO of the company. Moving forward, I plan to share my thoughts through CEO letters on an occasional basis, likely about once or twice a year.

As announced in our press release on December 23, 2024, I had the honor of being invited by Stanford University to speak at the 9th Center for Definitive and Curative Medicine (CDCM) Symposium on February 26, 2025. I would like to take this opportunity to share an overview of the event. The symposium took place at the Li Ka Shing Center for Learning and Knowledge, a venue frequently used for major events at the university campus.



Stanford's CDCM, held every year in February, invites leading researchers from the U.S. and around the world to give presentations on cutting-edge research in stem cell and regenerative medicine. These lectures are not only attended by Stanford faculty and staff but are also made publicly available online.

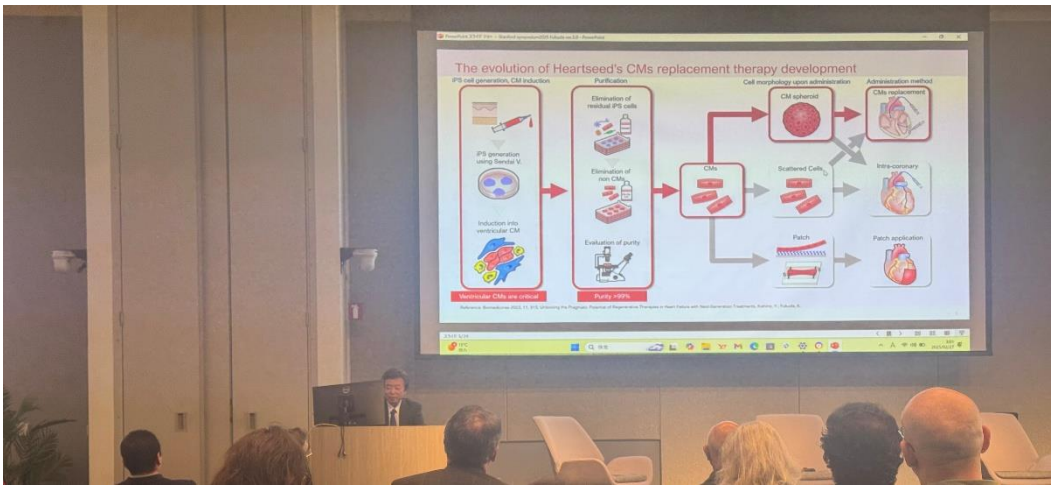
This year, I had the privilege of participating in a session titled "The Story of Cardiovascular Disease and the Promise of iPSCs", alongside two other distinguished speakers.

The first speaker was Professor Joseph C. Wu, Director of the Stanford Cardiovascular Institute and President of the American Heart Association (AHA). He is widely recognized as one of the world's foremost experts in the field. I have known Professor Wu since my time studying in the U.S., and for the past 30 years, we have been friendly rivals, pushing each other toward continuous innovation in the medical field. I also had the pleasure of inviting him to Japan twice for academic conferences in the past. In his presentation, he discussed his pioneering work on generating iPS cells from patients with various

heart diseases, differentiating them into cardiomyocytes, and screening drugs tailored to each condition. As a leading scientist in iPSC-based drug discovery for cardiovascular diseases, he has also founded Greenstone Biosciences Inc., a biotech dedicated to screening drug candidates for potential therapeutic applications. The second speaker was Dr. Mark A. Skylar-Scott, a promising scientist who recently joined Stanford University. His presentation focused on bio 3D printing technology, where he arranges vascular smooth muscle cells and endothelial cells to construct 3D vascular structures, layering pancreatic islet cells on top to create artificial tissues. His research has significant potential for future industrial applications.

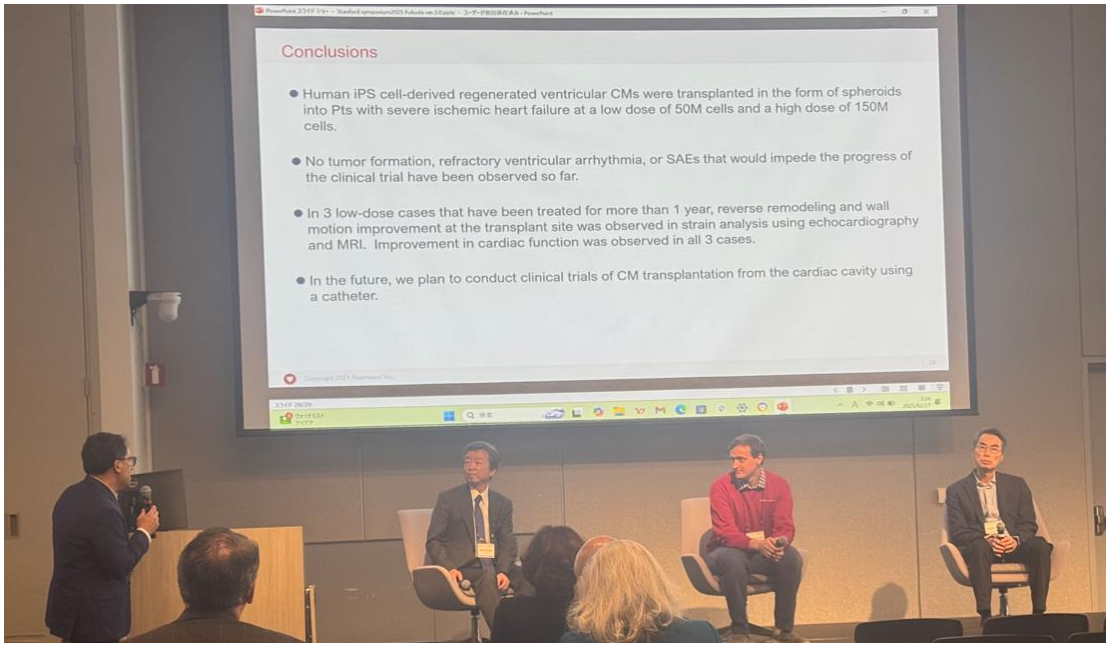
Following their presentations, I delivered my talk.

I introduced Heartseed's technology for differentiating iPSCs into ventricular cardiomyocytes, purifying them through metabolic selection, a method that removes residual undifferentiated iPS cells, and non-cardiomyocytes by leveraging the composition of the culture medium. I also explained how the engraftment efficiency of transplanted cardiomyocytes can be dramatically improved by forming cardiomyocyte spheroids, small aggregates of cardiomyocytes, and how we developed a specialized injection needle to minimize bleeding during transplantation.

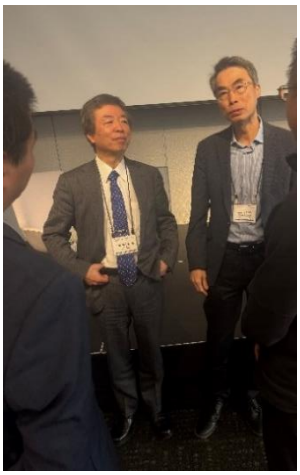


I also shared initial clinical findings reported by investigators at Tokyo Women's Medical University, where our cardiomyocyte replacement therapy is being tested. The five patients who received our cardiomyocyte spheroids transplantation there had extremely severe conditions in heart failure, with cardiac function even worse than that of patients with ischemic cardiomyopathy, a group with a historically high 10-year mortality rate of 62% in a past large-scale study (STICH Extension Trial). Among the three patients who have completed 1 year follow-up period as safety and efficacy endpoints, two showed an increase in ejection fraction on echocardiography, while MRI confirmed an increase in all three. NT-proBNP, a biomarker for heart failure, decreased in all three cases, indicating improvement. NYHA heart failure classification improved significantly in two patients, from Class III to Class I, while the remaining one patient improved from Class III to Class II at six months, though later returned to Class III due to following a COVID-19 infection before completing 1 year follow-up period. I also reported that transient accelerated idioventricular rhythms were observed in some of these five patients about two weeks after transplantation. However, they were asymptomatic and disappeared quickly without further complications.

After my presentation, several questions were raised. One researcher asked how I developed the metabolic selection method, widely is now widely used by researchers, including Dr. Skylar-Scott, for cardiomyocyte purification. Another inquired why Heartseed's transplantation approach had succeeded in overcoming ventricular arrhythmia issues, which have been a major challenge that many research groups have struggled with.



I explained that the idea for metabolic selection stemmed from the significant differences in metabolic enzyme expression between iPSCs and cardiomyocytes. I developed this method with the guidance of Professor Makoto Suematsu, a close friend who was then Dean of Keio University School of Medicine, using metabolomics analysis. Regarding Heartseed's success in transplantation safety up to date, I emphasized several key factors: our differentiation method produces only ventricular cardiomyocytes, ensuring high purity; our cardiomyocytes do not express HLA, reducing the risk of immune rejection; our cardiomyocytes spheroids transplantation minimizes necrotic cells, preventing inflammatory reactions; and our specialized injection needle with a "conical tip without bevel" reduces the risk of damaging the myocardium and blood vessels. These combined technological advancements would contribute enhancement of the safety of our therapy.



At the symposium, speakers were presented with commemorative gifts.

Following the event, I was invited to dinner with the other speakers.

At the dinner occasion, Dr. Skylar-Scott introduced me to fellow researchers seated nearby, mentioning that I was the scientist who invented and established metabolic selection using lactate-based purification. I was warmly received with applause and handshakes in recognition of this breakthrough. Beyond the symposium, I had the opportunity to engage with local biotech executives and researchers, deepening discussions about our science and technology. These interactions gave me further confidence in Heartseed's science and technology in the global competitive landscape.

I was also delighted to meet Japanese postdoctoral researchers studying at Stanford University. One physician who had treated patients awaiting heart transplantation expressed deep appreciation for Heartseed's work, saying he was moved by the early clinical results and hoped our therapy would save patients with no other options. Another researcher, aiming to implement his own research into a viable business, shared that the path I had opened up was very helpful and how he was deeply impressed by my efforts and challenges. They also remarked that Heartseed's current success is clearly built on an extensive and high-quality foundation of basic research data.

In recent years, fewer Japanese researchers have chosen to study abroad, and I am deeply concerned about the future of Japanese science. Research is the most powerful tool in advancing medicine, but it should not remain confined to academia. It must be implemented into real-world applications to benefit patients. By establishing a successful business model at Heartseed, I hope to inspire the next generation of researchers to pursue both scientific excellence and business implementation.

Lastly, I am fully aware of the high expectations our stakeholders have for Heartseed. We remain committed to delivering the best therapies through cutting-edge science. We will continue to provide updates on our business progress through PR and IR communications.
Thank you for your continued support.

Keiichi FUKUDA, MD/PhD/FACC
Heartseed Inc. CEO,
Representative Director of the Board