

## CellSeed, Inc.

**On the way to commercializing unique regenerative medicine products for postoperative esophageal stricture and for damaged joint cartilage**  
www.cellseed.com

CellSeed, Inc.  
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JAPAN

Founded in: 2001  
No. of employees: 20  
Type of Ownership: public  
Primary stock exchange: 7776

**December 2015:** Having leverage with its proprietary cell sheet engineering platform technology<sup>1</sup>, CellSeed is going to commercialize two products for which the regenerative medicine market has hardly waited.



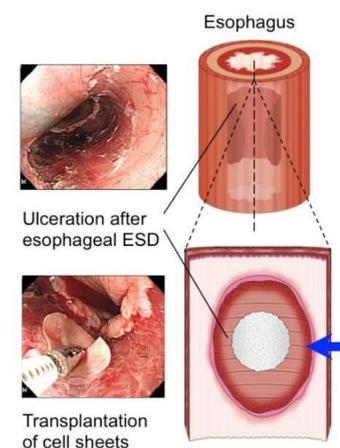
hardly waited for Venture Valuation (VV) interviewed the CEO, Dr. Setsuko Hashimoto.

**VV:** **CellSeed has been developing its first two regenerative medicine products. What is the status of each product?**

Hashimoto: For our first product, the epithelial cell sheet for esophageal regeneration, we have submitted the Investigational New Drug (IND) application to the Pharmaceuticals and Medical Devices Agency (PMDA). Once granted, hopefully early next year 2016, we will start Phase I clinical trials.

Along with the efficacy and the safety proven with 30 patients in clinical research in Japan and in Sweden<sup>2</sup>, we are hoping to benefit from the new regulatory framework<sup>3</sup> initiating “the conditional approval pathway”. This progressive process will allow us to proceed, at the PMDA’s discretion, to manufacturing and sales activities while the clinical trials (phase I, II, and III) are going on.

The epithelial cell sheet, which is cultured with patient’s own oral mucosal cells, is transplanted following the endoscopic submucosal dissection (ESD) procedure (see right). Our product protects patients against postoperative esophageal stricture, a major discomfort for them.



As for our second product, the regenerated cartilage sheet, clinical research was done with eight patients using each patient’s own

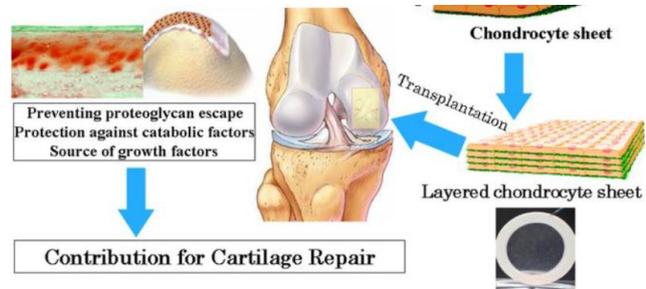
<sup>1</sup> Invented by Prof. Teruo Okano, Tokyo Women’s Medical University

<sup>2</sup> Karolinska University Hospital

<sup>3</sup> The new “Act on securing Safety of Regenerative Medicine” (ASRM) and the revised Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act were enacted in November 2014.

chondrocytes and synoviocytes in collaboration with Dr. Masato Sato, Tokai University School of Medicine.<sup>4</sup> All the patients who had multi-layered cell sheets transplanted have been steadily regaining their articular strength.

The cell sheet, as soon as transplanted, prevents proteoglycans from diffusing and keeps regenerating the cartilage (see right).



Preparation for the IND application is under way.

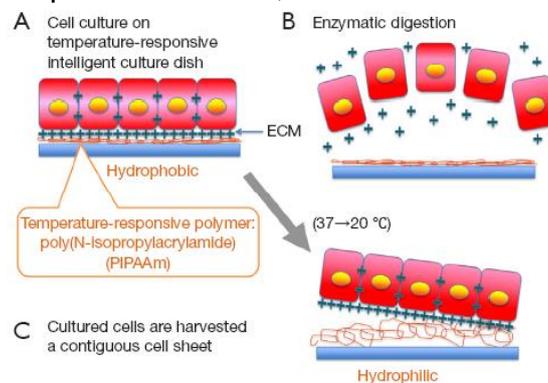
Moreover, Dr. Sato is planning clinical research in the use of allogeneic cells, permission having been granted by the Ministry of Health, Labor and Welfare.

**VV:** **CellSeed's core technology is cell sheet tissue engineering, a scaffold-free methodology. How is it different from the conventional approach?**

Hashimoto: The conventional cell culture method requires proteolytic enzyme treatment, which can damage cell-to-cell connections and the extracellular matrix (ECM). This is illustrated in Part "B" of the figure below. As a result, cells are unbound and broken up.

Our core technology, based on transplantable cell sheets made with a temperature-responsive polymer surface, has advanced the cell delivery process. This polymer, Poly(N-isopropylacrylamide), is hydrophobic as well as hydrophilic depending on the temperature.

As Part "C" of the figure below illustrates, "when cells are cultured on a temperature-responsive surface, the interconnection between ECM and



hydrophobic culture surface is released only by lowering temperature.

<sup>4</sup> Department of Orthopedic Surgery



Cell-to-cell connections are completely preserved and the cells are detached as a contiguous cell sheet. ECM retained underneath the cell sheets works as an adhesive agent.”<sup>5</sup>

The cell sheets, once cultured, are ready to be transplanted directly and regenerate the damaged tissue. They also have the advantage of creating thick tissues by being laid one on top to another.

Other than the epithelial cell sheet for esophageal regeneration and the cartilage regeneration, a variety of cell types have been cultured successfully. Corneal regeneration and periodontal tissue regeneration are being developed. Cardiac tissue regeneration developed by Terumo was approved in September 2015, which uses cell sheet technology.

**VV: The ASRM (Act on securing Safety of Regenerative Medicine) doesn't follow international guidelines such as GMP (Good Manufacturing Practice).**

Hashimoto: Because the production processes related to regenerative medicine and cell therapy have different requirements from drug products and active pharmaceutical products, the PMDA has established globally one and only guideline called the **GCTP** (Good Gene, Cellular, and Tissue-based Products).

The GCTP inspection is applied to manufacturing sites both in Japan and abroad. It may become an international standard guideline for regenerative medicine.

**VV: CellSeed is going to open a cell processing center (CPC).**

Hashimoto: In compliance with the ASRM, a bio-clean room named CPC is mandatory. Our 760m<sup>2</sup> CPC will be fully operational in summer 2016 in Tokyo Bay. Four culture rooms will handle ca. 100 cell culture projects per room annually. On average, cell culture for an epithelial cell sheet for esophageal regeneration takes two weeks, and a regenerated cartilage sheet three weeks.

Incidentally, our head office is going to move at the end of this year into the same building as the CPC site.

**VV: CellSeed is supplying its original temperature responsive cell cultureware products for research use.**

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<sup>5</sup> Kanai N, Yamato M, Okano T. Cell sheets engineering for esophageal regenerative medicine. Ann Transl Med 2014;2(3):28. doi: 10.3978/j.issn.2305-5839.2014.03.06 <http://www.atmjournals.org/article/view/3537/4381>



Hashimoto: The sales have been increasing year by year. We are focusing on designing and developing them while manufacturing is outsourced. Our worldwide distributor is Thermo Fischer Scientific. Our products are available through their website or their regional office wherever you are located.

**VV: What is your global strategy?**

Hashimoto: While our current top priority is to commercialize and promote two products in Japan, we are intending to get CellSeed Sweden AB (founded last May near Stockholm) organized for marketing, sales, and research and development functions in Europe.

**VV Comments after the interview:**

As a prominent part of the biotech industry, the regenerative medicine market in which CellSeed is positioned is expected to grow to 150 billion USD in 2050 from 24 billion USD in 2012 worldwide.<sup>6</sup> The market will keep thriving providing that regulatory restrictions, treatment costs, and cultural and ethical issues are dealt with.

Japan's new regulatory framework may contribute to the market growth and attract foreign companies to conduct clinical trials in Japan. A challenge for the PMDA is how to effectively promote the new regulatory framework and the GCTP internationally.

In the growing market environment, small-sized companies with remarkable technology but limited funds in Japan may have a great opportunity to partner with foreign companies who are willing to invest. To make this happen, Japanese small-sized companies should draw the global media attention by proactive marketing communications in English. Targeted and frequent announcements in English would help them be recognized as well as foreign companies to reach out.

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Venture Valuation specializes in independent assessment and valuation of technology-driven companies in growth industries, such as the Life Sciences (Biotech, Pharma, Medtech), ICT, Nanotech, Cleantech and Renewable Energy. In addition to valuation products, Venture Valuation offers high-quality, focused information services like the Global Life Sciences Database, Biotechgate.com and this "Let's Interview Series" with companies with interesting technologies and services. We select and interview thriving companies and organizations all over the world.

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<sup>6</sup> "Japan for Regenerative Medicine: New Business Opportunities" by CellSeed presentation on October 16, 2014