Regenerative Therapy 2 (2015) 2–5

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Forum report

Regenerative therapy by fusion of medicine and engineering: First-in-human clinical trials with induced pluripotent stem cells and cell sheet technology: A report of the Symposium of Regenerative Medicine for Patients

Keywords:
iPS cells
Regenerative therapy
Act on the Safety of Regenerative Medicine
Pharmaceuticals
Medical Devices and Other Therapeutic Products Act
Cell sheet techniques
Macular degeneration
Retinal pigmented epithelium (RPE)

A B S T R A C T

The Symposium of Regenerative Medicine for Patients, organized by the Japanese Society for Regenerative Medicine, was held on 28 September 2014 in Tokyo, Japan. The event provided an overview of the important areas of cell-based medicine, and highlighted the first-in-human clinical trial of induced pluripotent stem cell (iPSC)-derived products. Recent advances in regenerative medicine were also discussed, especially regarding the use of somatic cells such as chondrocytes, skeletal myocytes and cardiomyocytes under both the Act on the Safety of Regenerative Medicine, and the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act.
© 2015, The Japanese Society for Regenerative Medicine. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Objectives

The Symposium of Regenerative Medicine for Patients aimed to promote research in regenerative medicine to the scientific community, and inform the general public of the advances being made, by providing an important forum to discuss key issues and new research in the field. The event offered a valuable platform for sharing new ideas and the latest developments in basic research, clinical translation, industrial development and regulatory issues encompassing stem cell biology, cell engineering, tissue engineering, and regenerative medicine. The symposium played an important part in our overarching goal to develop suitable treatments for our patients as quickly and safely as we can.

2. Participants

The symposium brought together representatives from academia, medicine, industry, and government in Japan as well as many general citizens, with a total of approximately 1200 people in attendance.

3. Message from Japanese prime minister

Shinzo Abe, Prime Minister of Japan, delivered the opening address of the event. In his speech, Abe emphasized the importance of research and development (R&D) of pharmaceuticals and medical devices to treat diseases. He recounted his own personal experience of ulcerative colitis, which was successfully treated by a novel drug, and described his hope and optimism for the development of new drugs and regenerative medicine therapies in the future. The prime minister described that Japan is a world leader in stem cell science and the use of induced pluripotent stem cells (iPSCs). To further bolster Japan's research capabilities, Abe reaffirmed the Japanese government's decision to commit a budget of USD$1 billion over 10 years to stem cell science and regenerative medicine, and the introduction of two important new laws: the Act on the Safety of Regenerative Medicine, and the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act). Under these new laws, the development of medical techniques and devices is expected to accelerate. Prime Minister Abe concluded his speech with hopes that Japan's innovations and research will further contribute to the development of medicine around the world.

4. Interdisciplinary research area between biological science and engineering

Teruo Okano, President of Japan's Society for Regenerative Medicine and Editor-in-Chief of this journal, led a discussion about how regenerative medicine can be developed through the fusion of biological science and engineering. He used the example of automobile manufacture to illustrate his point: automobiles are manufactured in a series of parts, such as tires, and tires are made from rubber. Similarly, cells as raw materials are propagated ex vivo, and are used to generate parts of cell products, such as cardiomyocytes

Peer review under responsibility of the Japanese Society for Regenerative Medicine.

http://dx.doi.org/10.1016/j.reth.2015.07.002
2352-3204/© 2015, The Japanese Society for Regenerative Medicine. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

and hepatocytes. Tissues and organs are finally manufactured in cell processing centers or facilities, just as automobiles are put together at an assembly plant.

In the early 1990s, Okano and colleagues developed a novel technique to generate cell sheets by fusing knowledge of both engineering and cell biology [1,2]. Okano described how this cell sheet technique has been used in clinical studies to treat diseases of the eyes, esophagus, and joints at Osaka University, Tokyo Women's Medical University and Tokai University, respectively [3–5], and noted the important development of transport technology in Japan, which has made cell products more widely available to patients in rural areas of Japan. Okano discussed the need for innovations in high-volume manufacturing to treat larger numbers of patients and reduce production costs, and how automated devices are currently being developed by industry to address this need. He noted that from November 2014, commission of the manufacture of cell products in Japan will be permitted under the Act on the Safety of Regenerative Medicine. In addition, early conditional approval of cell product manufacture will commence under the Act on the Safety of Regenerative Medicine and PMD Act. Okano highlighted the importance of collaboration in the areas of biology, medicine and engineering to accumulate and broaden knowledge, enhance scientific and industrial development, and to strengthen an interdisciplinary approach in regenerative medicine research.

5. First-in-human clinical trial of iPSC-based therapy

Nobel prize-winning stem cell researcher Shinya Yamanaka gave a keynote lecture at the symposium and celebrated the first-in-human clinical trial using iPSCs led by Masayo Takahashi, a RIKEN researcher [6–8]. iPSCs are a type of pluripotent stem cell able to differentiate into multiple cell types such as neuron, hepatocyte, cardiomyocyte and beta cells [9].

Yamanaka described the aim of the Center for iPS Cell Research and Application (CiRA), where he is based, to start clinical trials using iPSCs, and examined the challenges involved in this work. Autologous iPSCs derived from patients are suitable as a means to avoid immunological rejection; however, it can take six months to generate iPSCs, differentiate them into target cells, and perform safety tests. Yamanaka also highlighted the cost of iPSC products, which can run up to several hundred thousand dollars for just one person.

In light of these challenges, Shinya Yamanaka talked about CiRA's plans to prepare a storage bank of iPSCs as raw materials of cell products from volunteers with homozygous HLA types; iPSCs from 75 people with different homozygous HLAs are considered to cover 80% of Japanese HLA types [10]. He outlined CiRA's four objectives to be achieved by 2020: (1) to advance iPSC technology and protect intellectual property; (2) to generate iPSC stock for regenerative medicine; (3) to commence a first-in-human clinical trial; and (4) to further drug discovery using patient iPSCs. In closing, Shinya Yamanaka stressed the need to reduce the transformation possibility of iPSC-derived products during manufacturing and after implantation, and drew attention to the fact that patients will be most affected by this drawback.

Next, Masayo Takahashi presented to the symposium details from her team's clinical trial of iPSCs in a patient with age-related macular degeneration. Macular degeneration is an intractable eye disease characterized by abnormal blood vessels growing beneath the retina. These new blood vessels leak fluid or blood that damages retinal pigmented epithelium (RPE) and photoreceptor cells, causing blurred or distorted central vision. The condition can be managed with an injection of an anti-angiogenic substance into the eyeball, which improves the symptomatic state during the early stages of the disease. Cell-based treatments are being developed to replace impaired RPE with intact RPE. In these treatments, RPE is prepared from iPSCs derived from a patient to prevent visual loss. The main purpose is to evaluate the safety of the iPSC-derived product and therapeutic procedure; in addition, tumorigenesis of the cell product is also being investigated [11]. Once the safety warranty is confirmed, the iPSC-derived RPE will be implanted at an early stage of the disease for further efficacy. In combination with low vision care and rehabilitation, iPSC-based therapy will provide better treatment for patients.

6. Chondrocyte product with scaffold

Symposium speakers went on to discuss regenerative medicine for patients with osteoarthritis, the most common form of arthritis. Osteoarthritis is a chronic condition in which cartilage that supports the joints breaks down and causes bone-on-bone friction. Approximately 10 million people suffer from osteoarthritis of the knee in Japan. As cartilage has limited regenerative capability due to its avascular nature or lack of blood vessels, cartilage regeneration is a key challenge in tissue engineering.

A Swedish group originally reported implantation of chondrocytes—a type of cell found in cartilage—after ex vivo propagation without scaffold [12]. Mitsuo Ochi's group combined chondrocytes with a scaffold, that is, ‘atelocollagen’ [13]. Chondrocyte/atelocollagen was commercialized by J-TEC Inc. after a clinical trial at Hiroshima University Hospital in April 2013, and it took 12 years to progress from an investigative new drug application to approval [14]. More sophisticated implantation techniques of the cell product still need to be developed [15]. To regenerate the auricle, nose, and chin bone, tissues or organs need to be generated. Tsuyoshi Takato emphasized the importance of innovation of human cellular and tissue-based products with a specific shape and stiffness [16]. By using 0.1 g of auricular cartilage, Takato and colleagues found that 6 cm of nasal cartilage can be successfully generated over 4 weeks' cultivation. In addition, auricles can also be generated. The symposium speakers reaffirmed that one of the final goals of regenerative medicine is to generate products such as tissues and organs, as well as cell suspension.

7. Cell sheet engineering

Using scaffolds may overcome the limitations of current techniques, including single-cell suspension injection. Yoshiki Sawa discussed how he and his colleagues developed a strategy to restore tissue functions using temperature-responsive cell culture surfaces [17]. The use of biodegradable polymer enabled transplantable cell sheets manufactured with temperature-responsive culture surfaces to be used for cell delivery. Cell sheet technology is currently being used in clinical studies for patients with otitis media, pyorrhea alveolaris, and cardiomyopathy. In 2000, Sawa collaborated with Teruo Okano, who originally developed temperature-responsive culture surfaces, and began a clinical study that applied the cell sheet technique using skeletal myocytes to a patient with cardiac failure [18,19]. The results revealed that efficacy of the skeletal myocyte sheet is comparable with organ transplantation. To increase the functionality of cell sheets, Sawa began research on cardiomyocyte sheets in collaboration with Shinya Yamanaka. iPSC-derived cardiomyocytes were found to be of an immature nature in vitro, however, in vivo maturation was detected after implantation.

Multi-layered cell sheets are currently under development to manufacture tissues and organs. Although single-cell sheets can be directly implanted onto tissues or organs, multi-layered cell sheets require vasculature. Tatsuya Shimizu and colleagues successfully generated multi-layered cardiomyocytes with a vascular network by adding endothelial cells [20,21]. These multi-layered

Download English Version:

https://daneshyari.com/en/article/2022360

Download Persian Version:

https://daneshyari.com/article/2022360

Daneshyari.com