

Perspectives on human clinical trials of therapies using iPS cells in Japan: Reaching the forefront of stem-cell therapies

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Summary

A research project involving sheets of retinal pigment epithelium constructed from iPS cells derived from patients with age-related maculopathy is one step closer to being approved for clinical trials by the Japanese Government. Now is the time to make therapies using iPS cells clinically available.

Keywords: Induced pluripotent stem cell, age-related maculopathy, clinical trial

In 2013, a therapy using induced pluripotent stem (iPS) cells progressed to the clinical trial stage in Japan. On February 28th, RIKEN and the Foundation for Biomedical Research and Innovation jointly applied for approval of a research project involving clinical trials of sheets of retinal pigment epithelium constructed from iPS cells derived from patients with age-related maculopathy. This project was reviewed by the committee of Health Science Council to review policies on clinical research involving human stem cells with an emphasis on safety and especially tumorigenesis. On June 26th, the Committee decided to approve this project with some provisos. If the Ministry of Health, Labor, and Welfare officially approves the project based on a decision by another committee on scientific technology, then the world's first clinical trial using material from patient-derived iPS cells may be conducted in the summer of 2014. This will bring Japan to the forefront of efforts to introduce a pioneering biomedical technology and benefit stem-cell therapies.

iPS cells were first generated from mouse mature skin cells by Prof. Shinya Yamanaka (Nobel laureate in 2012) of Kyoto University in Japan, and these cells have been used in basic studies worldwide. iPS cells have the ability to differentiate into various types of

somatic cells and can be used to construct functional cell sheets and tissue for transplantation. *In vivo* studies have raised concerns about the usage of iPS cells in that they may induce the formation of tumors, but improved gene transfer method has helped to increase the safety of this technology. In August 2012, Prof. Yamanaka proposed establishment of a standard assay system and cell bank of iPS cells (1). The RIKEN Bio-Resource Center began providing established iPS cells to non-profit researchers. This system helps to enhance the quality and speed of iPS cell research. Basic studies have been performed using the cell bank system. The cell bank system is a promising way to store and maintain iPS cells derived from individual patients.

A large program was launched in Japan starting in 2012 to support several long-term projects to facilitate the clinical use of iPS cell therapies (Table 1); the program is budgeted tens of millions of dollars every year. One of these long-term projects is studying age-related maculopathy, and the project is the first to apply to the government for approval of clinical trials. Age-related maculopathy is the leading cause of permanent blindness in the elderly and affects the central area of the retina, which is essential for central and color vision (2,3). The current treatment, administration of an anti-vascular endothelial growth factor receptor drug such as bevacizumab, alleviates symptoms but does not cure the condition. Retinitis pigmentosa is the main cause of blindness or visual impairment, so replacement of diseased retinal cells should be an effective treatment. Over the past few years, a research group led by Dr. Masayo Takahashi of the Center for Developmental

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Table 1. Main projects to implement regenerative medicine in Japan

Research topic	Institute/facility responsible
Development of therapies for age-related maculopathy by transplantation of retinal pigment epithelial cells established from iPS cells	RIKEN
Regeneration of the knee meniscus using synovial stem cells	Tokyo Medical and Dental University
Achieving regenerative medicine for the corneal endothelium by transplantation of cultured human corneal endothelial cells	Kyoto Prefectural University of Medicine
Development of less invasive liver regeneration therapies using cultured human bone marrow cells	Yamaguchi University
Development of regenerative therapies for the cornea using iPS cells	Osaka University
Establishment of therapies for serious heart failure by transplantation of regenerated heart myocytes derived from autologous iPS cells	Keio University
Clinical study of drugs derived from human embryonic stem cells to treat congenital metabolic disorders with severe hyperammonemia	National Center for Child Health and Development Kyoto University
Development of stem cell transplantation therapies for Parkinson's disease	

Biology of RIKEN has developed a novel method to construct retinal cells from human iPS cells (4). The group's most recent study examined the Ca²⁺ response and electrophysiological properties of developing and grafted rods and it established a way to evaluate the activation of transplanted rods (5). The researchers concluded that grafted cells function as rods and that rods derived from iPS cells *in vitro* may provide a renewable source for cell replacement therapy. The long-term project on age-related maculopathy is seeking to conduct clinical trials on sheets of retinal pigment epithelium constructed from iPS cells derived from patients with the condition. This project should offer insights into iPS cells and their clinical use in the near future.

Another project to facilitate the clinical use of iPS cell therapies involves the development of therapies for Parkinson's disease with the support of the Japanese Government. A research group led by Prof. Jun Takahashi of Kyoto University showed that dopaminergic neurons differentiated from human iPS cells under feeder-free and serum-free conditions and that these neurons survived in a primate model of Parkinson's disease (6). Prof. Takahashi expressed his intent to apply for approval of a clinical trial of a novel therapy for Parkinson's disease involving transplantation of iPS cell-derived dopaminergic neurons in 2014, if all goes smoothly.

Advances in stem-cell therapies have been early awaited worldwide for several decades now. The large program launched in 2012 in Japan with the support of the Japanese Government will play a key role in facilitating the clinical use of iPS cell therapies. Currently, the Ministry of Health, Labor, and Welfare of

Japan is considering approval of clinical trials of sheets of retinal pigment epithelium constructed from iPS cells derived from patients with age-related maculopathy, and the Ministry's approval of clinical trials of a therapy for Parkinson's disease using iPS cell-derived neurons will soon be sought. "Now is the time to make therapies using iPS cells clinically available."

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