Frontiers in Regenerative Medicine

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Regenerative Medicine Realization Highway

The branch of medicine that aims to restore the dysfunction tissues and organs in vivo by utilizing cells is termed "regenerative medicine", and its early realization is desired.
A brief overview of the current state of regenerative medicine research in Japan is presented below.

Concept of "Regenerative Medicine Realization Highway"

Regenerative medicine research in Japan had been promoted nearly independently by The Ministry of Education, Culture, Sports, Science and Technology, The Ministry of Health, Labour and Welfare, and The Ministry of Economy, Trade and Industry since approximately 2002 or 2003. The establishment of the Japan Agency for Medical Research and Development in Spring 2015 has enabled unified management of research and development budgets from these 3 ministries and led to the organization of a seamless support system, the "Regenerative Medicine Realization Highway", covering various aspects from basic research to practical application (Figure 1). Additionally, 3 acts on regenerative medicine enacted in 2013 have provided the basis for a clear policy that aims at industrialization of innovative findings in regenerative medicine involving an all-Japan system.

The FY 2015 budget (14.3 billion yen) has been promoting research and development organized under 2 major frameworks: "Regenerative Medicine Realization" and "Utilization in Drug Discovery, etc." Approximately 75% and 20% of the budget are allocated to the study of pluripotent stem cells (iPS and ES cells) and somatic stem cells, respectively. For research and development steps, approximately 80% of the funds is distributed to basic and pre-clinical research, while 20% is distributed to clinical research and clinical trials. The main program, "Research Center Network for Realization of Regenerative Medicine", plans to distribute HLA-homozygous iPS cells for clinical use prepared at the Center for iPS Cell Research and Application (CiRA), Kyoto University to individual disease-/tissue-specific centers for cardiac muscle (Osaka University), spinal injury (Keio University), Parkinson’s disease (Kyoto University), eye (RIKEN), diabetes mellitus (University of Tokyo), liver (Yokohama City University), articular cartilage (Kyoto University), cancer (RIKEN and Yokohama City University), and intestine (Tokyo Medical and Dental University) for induction of differentiation into target cells and clinical application at individual centers. In parallel, 20 specific technical tasks (covering culture technologies, scaffold materials, quality control, and laboratory animals for studies of regenerative medicine, etc.) are being developed in collaboration with the industry. As a part of the "Research Project for Practical Applications of Regenerative Medicine," a project involving platelet production from iPS cells (Kyoto University), has successfully prepared 1011 platelets. The greatest challenge in the clinical application of iPS/ES cells is safety assurance, particularly the control of stem cell tumorigenicity. Our attempt at using regenerative medicine for the treatment of retinal degenerative diseases (RIKEN Kobe Institute) successfully transplanted 105 retinal pigment epithelial cells of iPS origin confirmed to be free of other cell types; to the best of our knowledge, this is the first such attempt. However, obtaining 109 retinal pigment epithelial cells free of other cell types remains beyond the current technical.

Numerous cell therapies investigated in the "Research Project for Practical Applications of Regenerative Medicine" have been evaluated in clinical trials, including liver regeneration therapy with interstitial cells isolated from autologous adipose tissue for the treatment of hepatic cirrhosis and transplantation of cardiac stem cells in pediatric heart failure. Both use somatic stem cells.

The Disease-Specific iPS Cell Project involves the establishment of iPS cells from patients with various refractory diseases, induction of differentiation to target cells in vitro to reproduce the pathology, screening of drugs to correct abnormalities, and drug discovery. For example, the effectiveness of a statin in achondroplasia has been published as a breakthrough.
### Concept of "Regenerative Medicine Realization Highway"

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<td>Discovery, etc.</td>
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#### Goals to be achieved by FY 2015
- Number of research projects using human stem cells proceeding to clinical studies/trials: approximately 10 (examples: age-related macular degeneration, corneal diseases, knee meniscal tear, bone/cartilage reconstruction, hematological disorders)
- Development of drug discovery technology using IPS cells

#### Goals to be achieved by approximately 2020
- Clinical application of new therapeutic drugs prepared by utilizing IPS cell technology
- Increase in number of regulatory approvals granted to regenerative medical products
- Extension of target diseases for regenerative medicine subjected to clinical studies or clinical trials (approximately 15 studies/trials*)
- Practical realization of peripheral devices/equipment related to regenerative medicine
- Proposal for international standardization of evaluation methods for drug cardiotoxicity applying IPS cell technology

*Include 10 studies/trials referred to in "Goals to be achieved by FY 2015"
iPS Cell Research Road Map

A revised version of the iPS cell research road map published in November 2015 by the Task Force on Strategies for Stem Cells and Regenerative Medicine, The Ministry of Education, Culture, Sports, Science and Technology describes the timing of clinical application predicted for individual tissues and organs generated from iPS cells. This varies between both tissues and organs depending on the difficulty in inducing differentiation from stem cells and subsequent organ construction. Whether the first-in-man application will be a clinical study (under the Act on the Safety of Regenerative Medicine) or a clinical trial (under the Pharmaceuticals and Medical Devices Act) is currently unknown, and attention should be given to future trends to determine which type of evaluation will be conducted. The involvement of companies in projects aiming at the clinical application of regenerative medicine may be another determinant. Generally, in Japan, the number of venture companies is small and major companies are slow to act because of their policies that value prudence.
Future tasks

While production of a single type of cells (e.g., retinal pigment epithelial cells, platelets) from iPS cells has been achieved, 3-dimensional construction of organs containing multiple types of cells (e.g., liver, kidney) or preparation of tissues containing vessels, nerves, and interstitium (stroma) demands further innovation. In addition, the superiority to conventional treatment in safety, efficacy, and cost is needed. Furthermore, industrialization that enables low-cost, large-scale production is indispensable for dissemination of these methods as healthcare technology. Application to drug discovery is a unique advantage of iPS cells over ES cells, and somatic stem cells and will be investigated more extensively in the future. Application of iPS cells to drug discovery is a field involving intensive global competition.