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Review

Recent policies that support clinical application of induced pluripotent stem cell-based regenerative therapies☆

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ABSTRACT

In Japan, a research center network consisting of Kyoto University to provide clinical-grade induced Pluripotent Stem Cells (iPSC) and several major research centers to develop iPSC-based regenerative therapies was formed for the clinical application of iPSCs. This network is under the supervision of a newly formed funding agency, the Japan Agency for Medical Research and Development. In parallel, regulatory authorities of Japan, including the Ministry of Health, Labour and Welfare, and Pharmaceuticals and Medical Devices Agency, are trying to accelerate the development process of regenerative medicine products (RMPs) by several initiatives: 1) introduction of a conditional and time-limited approval scheme only applicable to RMPs under the revised Pharmaceuticals and Medical Devices Act, 2) expansion of a consultation program at the early stage of development, 3) establishment of guidelines to support efficient development and review and 4) enhancement of post-market safety measures such as introduction of patient registries and setting user requirements with cooperation from relevant academic societies and experts. Ultimately, the establishment of a global network among iPSC banks that derives clinical-grade iPSCs from human leukocyte antigens homozygous donors has been proposed. In order to share clinical-grade iPSCs globally and to facilitate global development of iPSC-based RMPs, it will be necessary to promote regulatory harmonization and to establish common standards related to iPSCs and differentiated cells based on scientific evidence.

1. Introduction

Induced pluripotent stem cells (iPSCs) were firstly made from mice in 2006 [1] and from humans in 2007 [2,3]. iPSCs share many characteristics with embryonic stem cells (ESCs), including the ability to self-renew and differentiate into all cell types of the adult body. However, because iPSCs are made not from a fertilized egg but from somatic cells, their creation avoids the destruction of fertilized eggs and allows them to be acquired from donors whose genetic characteristics and other health records are already well

Abbreviations: iPSC, induced pluripotent stem cell; ESC, embryonic stem cell; HLA, human leukocyte antigen; RMP, regenerative medicine product; R&D, research and development; AMED, Japan Agency for Medical Research and Development; MEXT, Ministry of Education, Culture, Sports, Science and Technology; MHLW, Ministry of Health, Labour and Welfare; METI, Ministry of Economy, Trade and Industry; JST, Japan Science and Technology Agency; NIBIO, National Institute of Biomedical Innovation; NEDO, New Energy and Industrial Technology Development Organization; FY, fiscal year; CiRA, Center for iPS Cell Research and Application; IRB, Institutional Review Board; RM Act, the Act on the Safety of Regenerative Medicine; Riken CDB, Riken Center for Developmental Biology; IBRI, Institution of Biomedical Research and Innovation; PMDA, Pharmaceuticals and Medical Devices Agency; NIHS, National Institute of Health Science; PAL, Pharmaceutical Affairs Law; PMD Act, Pharmaceuticals and Medical Devices Act; GMP, good manufacturing practice; GCTP, Good Gene, Cell, Cellular and Tissue-based Products Manufacturing Practice; DMF, Drug Master File; LVAD, left ventricular assist device; J-MACS, Japanese Registry for Mechanically Assisted Circulatory Support; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; U.S., United States; GAiT, Global Alliance for iPS Cell Therapies; WHO, World Health Organization; CFR, Code of Federal Regulations; FDA, Food and Drug Administration; BLA, Biological License Approval; IND, Investigational New Drug; ICH, The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; PIC/S, The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme.

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documented. Like ESCs, iPSC-based products are used as research tools for drug toxicity testing, such as drug-induced QT prolongation [4–6]. A unique application of iPSCs is that they can be derived from diseased patients, which gives them a distinct advantage over ESCs for disease modeling and drug discovery [7–21].

Regarding cell therapy applications, it is expected that iPSC-based products from healthy donors can be used for allogeneic therapies. By carefully selecting donors that have homozygous human leukocyte antigens (HLA), it will be possible to reduce immune rejection and thus also the dose of immunosuppressive agents [22–35]. In addition, iPSCs have the potential for autologous therapies, further reducing the risk of immune rejection [36,37].

In Japan, the discovery of iPSCs has stimulated strong government support for the development and commercialization of iPSC-based technology, including generous research funding. This support was amplified after the Nobel Prize in Physiology or Medicine was awarded in 2012. In addition, regulatory authorities have reevaluated policy in order to facilitate effective and efficient regulatory clearance for marketing approval of this technology [38–45]. In this manuscript, we will review relevant policies and collaborative efforts among academia, industry and government agencies. We also discuss potential regulatory and ethical challenges related to future international cooperation for HLA homozygous iPSC banks, which are being used as sources for iPSC-based regenerative medicine products (RMPs).

2. Role of public funding to facilitate R&D on iPSC-based regenerative therapies

2.1. Establishment of Japan Agency for Medical Research and Development

In order to promote medical research and development (R&D), including regenerative medicine, the Japan Agency for Medical Research and Development (AMED) was established as a new National Research and Development Agency on April 2015 [40,43,46]. AMED is organized to consolidate national medical R&D funding, which was previously operated directly by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Health, Labour and Welfare (MHLW) and Ministry of Economy, Trade and Industry (METI) or through the Japan Science and Technology Agency (JST), National Institute of Biomedical Innovation (NIBIO) and New Energy and Industrial Technology Development Organization (NEDO) [47]. AMED also consolidates the operation of the research center network for realization of regenerative medicine (fiscal year (FY) 2015 budget: 8.99 billion yen) from MEXT, regenerative medicine clinical application program (FY2015 budget: 2.78 billion yen) from MHLW and regenerative medicine industrial technology development support program (FY2015 budget: 2.5 billion yen) from METI (Fig. 1) [48,49].

2.2. Collaboration for regenerative medicine related to the iPSC stock project

For R&D toward iPSC-based regenerative therapies, close collaboration between research centers that generate and provide (or distribute) iPSCs and those that differentiate iPSCs into final products are important. Therefore, MEXT and JST initiated a new program, “Research center network for realization of regenerative medicine” in FY 2013 (Fig. 2) [50]. Under this program, the Center for iPS Cell Research and Application (CiRA), Kyoto University, was selected as a core center for iPSC research to conduct “iPSC stock development projects for regenerative medicine”. Four research centers (Keio University, CiRA, Riken and Osaka University) were selected as “Centers for Clinical Application Research on Specific Disease/Organ (Type A Centers/Institutions)”, which aim at the clinical application of iPSC-based regenerative therapies by FY 2017, making them national leaders in iPSC-based regenerative therapy R&D. Overall, the program consists of many other iPSC-based regenerative therapy R&D projects. Table 1 shows examples of disease/organ research projects related to iPSC-based regenerative therapy being done by at least one of the four institutions under this program. Many of these projects involve collaborations using the iPSC stocks provided by CiRA.

One of the primary roles of CiRA is to provide seed stocks of iPSCs for the development of therapeutic products [51–53]. The stock generated from HLA-homozygous donors is expected to reduce the risk of immune rejection upon the transplantation of differentiated cells to recipients having the same HLA haplotype [22–35]. Therefore, CiRA is developing a series of clinical grade iPSCs from HLA-homozygous donors in collaboration with the Japan Red Cross, the Japan Marrow Donor Program and cord blood banks.

In general, user research centers will expand and establish their own cell banks of iPSCs or of downstream stem/progenitor cells for pre-clinical and clinical studies. In the case that the research center derives iPSCs from a source other than the CiRA iPSC stock for therapeutic purposes, CiRA will provide technical assistance when necessary. For example, the two institutes will characterize and analyze the iPSC-based differentiated cells together. For the development of iPSC-based regenerative therapy, in addition to general pre-clinical toxicity testing, additional consideration of tumorigenicity related to residual undifferentiated cells, contaminant cells, cells genetically transformed to malignancy during culture, or residual vectors is essential [54–63]. The relationship between genomic abnormalities of iPSCs or final products and tumorigenicity is not yet elucidated. To appropriately analyze genomic abnormalities of the final products, it is necessary to compare genome information from the original donor cells, iPSCs and differentiated cells. CiRA will be responsible for the genome analysis, and user research centers will be responsible for tumorigenicity studies. The results of these works will be used to optimize quality standards for both iPSCs as raw material and differentiated cells as final products.

2.3. Expansion of clinical research infrastructure

To facilitate academia-based clinical research of iPSC-based regenerative therapies, collaboration with hospitals that have experts who can prepare clinical research protocols and manage clinical research, is important. Therefore, MHLW and MEXT started several grants for clinical research infrastructure [40]. These grants facilitate early-phase and exploratory clinical trials using iPSC-based regenerative therapies. Osaka University and Keio University Hospitals have been awarded the early/exploratory clinical trial center grant since 2011 [64], and Kyoto University Hospital the clinical research core center grant since 2012 [65]. MHLW certified Institutional Review Boards (IRBs) at these three institutions in April 2015 based on a new certification program [66]. Osaka, Keio and Kyoto Universities also established specially certified regenerative medicine committees to review clinical research protocols for iPSC-based therapies under the new Act on the Safety of Regenerative Medicine (RM Act) enacted in November 2014 [39,43,67,68]. Although the Center for Developmental Biology (CDB), Riken, does not have its own hospital, it has already begun iPSC-based retinal pigment epithelium (RPE) clinical research by coordinating with Institution of Biomedical Research and Innovation (IBRI) Hospital, which has been awarded the Japan initiated global trial center grant since 2012 [69]. These grants were transferred from MHLW to