

Induced pluripotent stem cells are Japanese brand sources for therapeutic cells to pretrial clinical research

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ABSTRACT

iPSCs are promising and have potential benefits for medical use, understanding human organogenesis, and cell therapy for advanced diseases. iPSCs are derived pluripotent cells which can further differentiate into functional human cell-lineages, such as neuronal, epithelial cells, cardiac cell, immune cell, and blood cells, etc. Thirteen years on, the discovery of iPSC has revolutionized the field of regenerative medicine, and also the number of clinical studies using iPSC has been growing rapidly worldwide. However, Japan is leading the race of iPSC-based studies and clinical trials due to government support. The Japanese government implemented the world's fastest approval system and set to host first pretrial clinical studies using iPSC derived therapeutic products. Also, multinational companies of Japan are investing enormously in iPSC-based research for mobilization of iPSC-derived regenerative products to the research institution globally. This review presents an overview of iPSCs, potential benefits, commercialization of iPSC, iPSC-based pretrial clinical studies, and iPSC biobanking in Japan.

Key words: Induced pluripotent stem cells, therapeutic cells, clinical trials, biobank, Japan

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INTRODUCTION

Induced pluripotent stem cells (iPSCs) are reprogrammed pluripotent cells that acquire potential sources of therapeutic cells, such as retinal pigment epithelium (RPE), neurons, and cardiomyocytes, etc.¹. iPSC technology is a state of changing the plasticity of differentiated cells to a pluripotent state by ectopic expression of defined transcription factors (Oct4, Sox2, Klf4, and c-Myc)^{2,3}. These cells were generated from differentiated somatic cells, such as blood cells, fibroblast, keratinocyte, and urine cells, etc.⁴. Also, other differentiated cell types and transcription factors used for generating iPSCs are available in the online database⁵. They have characteristic properties, like self-renewal and pluripotency, that can proliferate indefinitely and differentiate into an amalgam of developmental germ layers^{2,3}. These cells widen the range of application in biomedical research, which was used to study organoidogenesis, and generation of clinical-grade therapeutic cells for replacement therapy^{6,7}. Such iPSC-derivatives become the hope for many patients to improve their health.

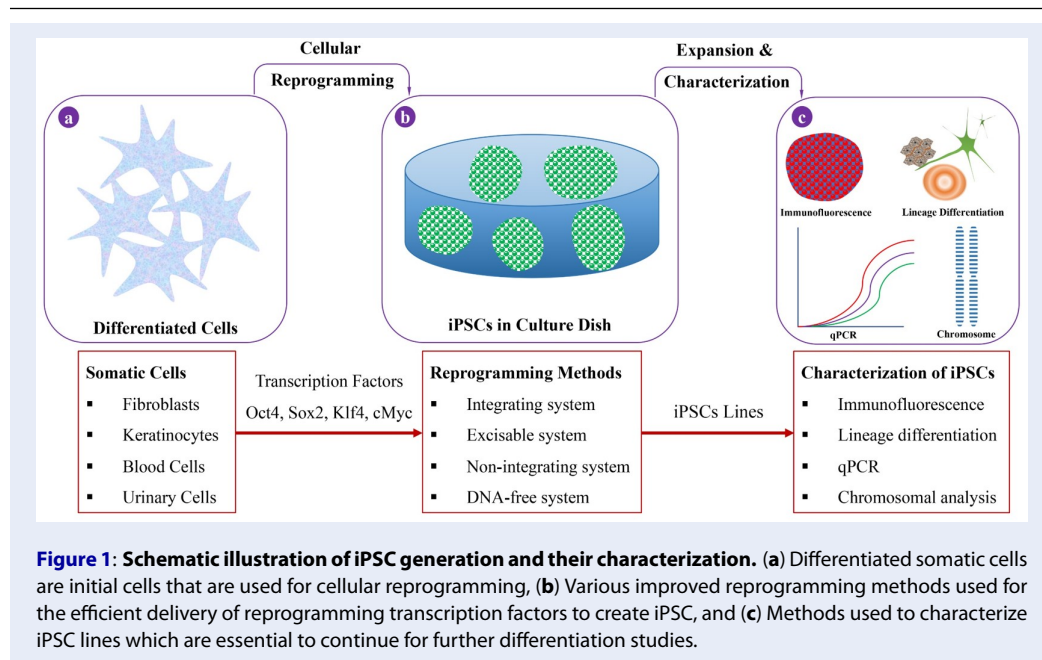
As noted above, the four defined transcription factors were delivered using retroviral vectors to generate iPSCs. Thereafter, various improved delivery methods including integrating system (lentiviral, and inducible lentiviral), excisable system (transposon,

loxP-flanked lentiviral), nonintegrating system (adenoviral, Sendai virus, episomal plasmid), and DNA free system (recombinant proteins system, modified mRNA transfection, microRNA) were used to deliver reprogramming factors^{8,9}, as shown in **Figure 1**. In addition, several small molecules and soluble factors such as valproic acid, sodium butyrate, BIX-01294, SB431542, vitamin C, Y-27632, and PS48 have been used to enhance the efficiency of iPSCs production⁹. The study is based on the analysis of relevant peer-reviewed and published literature for this review on iPSCs-derived therapeutic cells. All the information was obtained from the reliable literature sources, such as PubMed, Science Direct, Nature News, institutional websites, and other authenticated public domains. Several search terms like iPSCs, genomic instability, therapeutic cells, clinical trials, and Japan were used to find suitable documents. "Boolean operators" (AND, OR, NOT) were used between search terms to retrieve literature from PubMed. In this review, we primarily focus on the therapeutic potential of iPSC derivatives, iPSC technology commercialization, clinical studies, iPSC biobanking, and ongoing research using iPSCs in Japan.

iPSCs as a source of therapeutic cells

iPSCs offer a promising platform for cell-based therapy and personalized medicine. It was a breakthrough

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in the field of regenerative medicine that was discovered by Shinya Yamanaka and his colleagues in 2006². His innovation of iPSCs led him to be honored with Nobel Prize in Physiology or Medicine 2012 (jointly awarded with Sir John B Gurdon)¹⁰. iPSCs derivatives are potential therapeutic cells that overcome the limitation of ethical issues and immune barriers associated with embryonic stem cells (ESCs)¹¹. In a decade, iPSC became the brand source of Japan that flourished globally due to its potential benefits in disease modeling, regenerative therapy, drug screening, population health, and basic research⁷. Known that iPSC-derived cells have been gaining high demand for therapeutic use in the clinic, it is essential to determine the genomic integrity that could be associated with forced reprogramming, selective pressure, and cultural adaptation^{12,13}. Several studies reported the possibility of recurrent genomic alterations in iPSCs, such as cytogenetic abnormalities and copy number variations (CNV) that raise the potential safety issues¹⁴⁻¹⁸. However, considerable evidence indicates that genomic heterogeneity in iPSCs was inherited from the parental cells carrying somatic mutations that have a random probability distribution. Such genetic variations are neither due to reprogramming nor does it lead to an increased number of de novo mutations. They reported that observed rare alterations in parental cells existed in low frequencies detected by sequencing-based approaches^{19,20}. These indicate iPSC reprogramming is not mutagenic that supports the safety considerations for product development and the therapeutic application of iPSC-derived

cells in regenerative medicine, as illustrated in **Figure 2**. iPSC technology offers several advantages that can be used directly for the study of developmental biology, disease modeling, drug discovery, and cell transplantation⁹. Although iPSCs have benefits in regenerative medicine, they do have some disadvantages, as listed in **Table 1**.

Meanwhile, genomic instability (chromosomal alterations, CNVs, and mutations) in iPSCs are major concern in clinical applications, but the key factors governing the instability is still elusive^{9,12,18}. Instability in iPSCs are similar to that seen in cancer cells, which have compromised cell therapy safety²¹. Such transient mutation can be reduced by using starting cell sources from the younger donor, avoiding oncogenic transcription factors, using non-integrating vectors system, chemical induction, and using antioxidants in the culture medium^{9,12}. Also, high-resolution SNP genotyping should use to classify mutation pattern, differentiate benign mutations, and those causing tumor formations to mitigate effects of these mutations on cell therapy²².

iPSC technology commercialization in Japan

In a short time, iPSC benefits were well-recognized for medicine in the global community. Thus, iPS Academia Japan, Inc. was established at Kyoto University on 25 June 2008 to govern the licensing of iPSC patents, and then promote iPSCs and related technology transfer to industry for its commercialization²³.

Table 1: Advantages and disadvantages of iPSCs in stem cell-based medicine

S.N.	Advantages	Disadvantages
1.	iPSCs are readily available and have the potential to differentiate into therapeutic cells like RPE, neurons, and cardiomyocytes.	iPSCs generation is time-consuming, expensive, and some transcription factors used in reprogramming are oncogenic.
2.	iPSCs can be differentiated to organoids that closely mimic the human organs that are inaccessible to investigate, like retina and brain.	Reprogramming efficiency is low and also depends on the types of somatic cells used for reprogramming.
3.	iPSCs-derived specific cells can be used to screen various candidate drugs for personalized medicine.	Viral vector-based reprogramming has the potential to develop tumorigenesis when transplanted.
4.	Patient-specific iPSCs can be used to model human genetic diseases.	Forced reprogramming and long-term cultural adaptation induce genetic mutations in iPSCs.
5.	Like ESCs, iPSCs have no moral and ethical issues as it is derived from the patient's somatic cells.	Allogenic transplantation of iPSC-derived therapeutic cells causes the rejection of transplants.

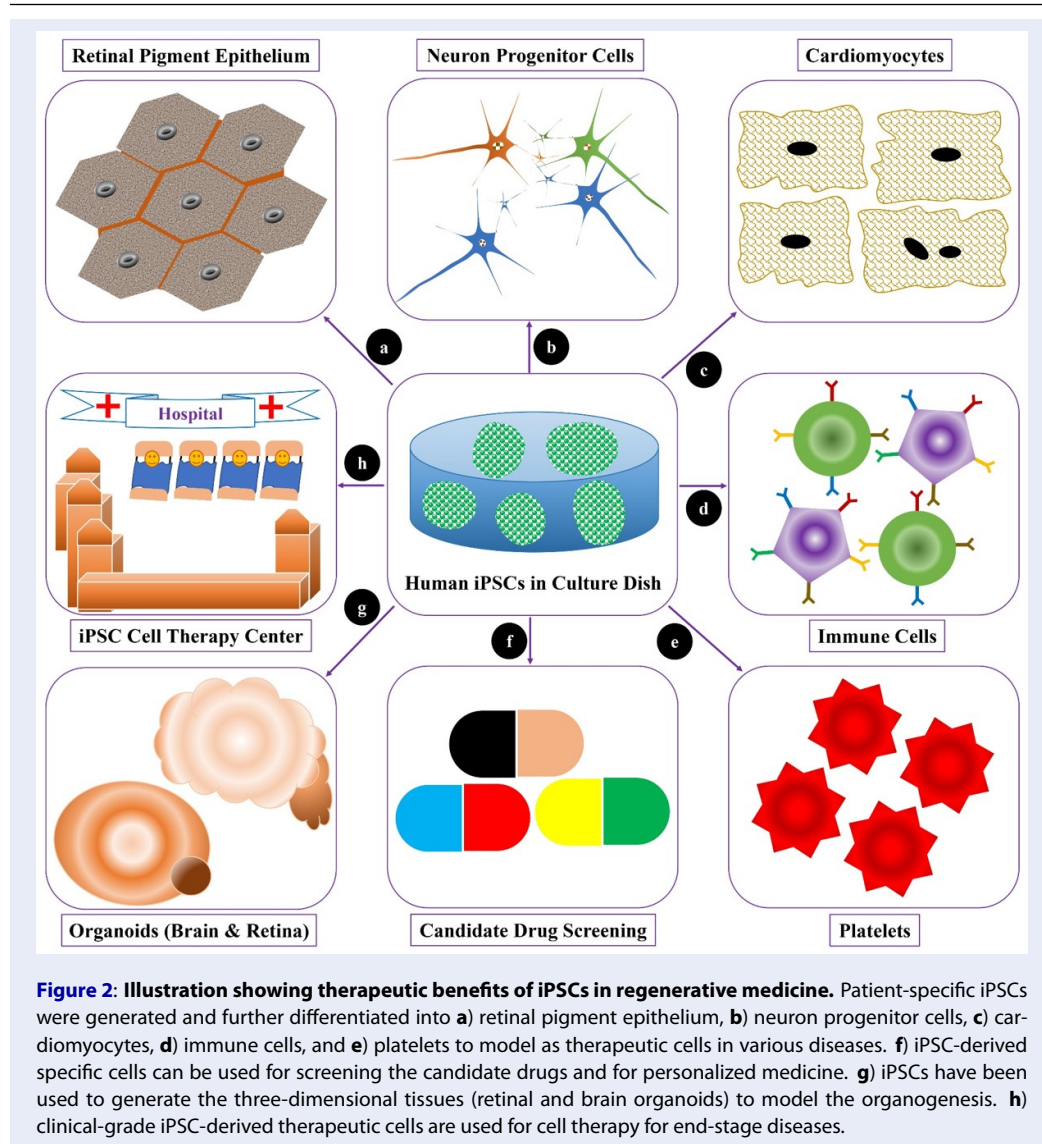
In 2009, the first license agreement was signed with ReproCELL and then with Cellular Dynamics International in 2010 for industrialization of technology to generate clinical-grade iPSC. Later, Fujifilm acquired Cellular Dynamics International (CDI) and invested significantly in stem cells to develop safer and efficient iPSC-based cell therapies²³. Now, Fujifilm headquartered in Tokyo is the foremost leader in the field of regenerative medicine. Afterward, license agreements have been signed with numerous companies globally that include 110 in Japan, 46 in North America, 34 in Europe and 5 in Asia as of April 2019²⁴.

The fact that iPSCs could be generated from the adult cells without moral and ethical restrictions, these cells have been showing potential benefits and growing impact in medicine. Also, iPSC-based clinical studies have been receiving growing scientific interest and rapidly increasing in number worldwide. Thus, the commercialization of these cells represents the productive market in the field of regenerative medicine. Knowing the progressive impact on medicine, Center for iPS Cell Research and Application (CiRA) was established in 2008 to hold the intellectual property and to foster iPSC technology. Later, on 1 April 2010, CiRA was recognized as an independent institute at Kyoto University and Nobel Laureate, Shinya Yamanaka was appointed as a director²⁵. Currently, CiRA grips basic iPSC technology patents in numerous countries, such as Australia, Canada, China, France, Germany, Ireland, Italy, Japan, Mexico, Singapore, Spain, Sweden, UK, and U.S. *etc.*²⁶. In addition, CiRA promotes the iPSC stock, iPSC-based cell therapy, and personalized medicine using iPSC cells. Due to the high demand of iPSC-based clinical studies, the iPS Cell Stock for Regenerative Medicine

project was started in 2013. Further, they established the Facility for iPS Cell Therapy (FiT) to support the distribution of clinical-grade iPSC to institutions for developing new medical therapies. Later in February 2017, Japanese pharmaceutical company, Sumitomo Dainippon Pharma Co., LTD. started the construction of manufacturing plant for regenerative medicine and cell therapy to accelerate iPSC research and the advancement of iPSC therapies into the clinic. The Sumitomo Dainippon Manufacturing Plant for Regenerative Medicine & Cell Therapy (SMaRT) was established in its Central Research Laboratories at Osaka, Japan. The manufacturing plant, which cost around 3.6 billion Yen, was completed on 1 March 2018. There onwards, the plant is engaged in generating iPSC derivatives for the treatment of age-related macular degeneration (AMD), retinitis pigments, spinal cord injury, and Parkinson's disease *etc.*²⁷.

iPSC-based pretrial clinical studies in Japan

Thirteen years on, safety, efficacy, and potential benefits of iPSC derivatives has been proved in preclinical models. iPSC is an innovation of Japan, now leading for quality commercialization of iPSC-derivatives, and also becoming the world first nation to conduct pretrial clinical studies. Japanese researchers consider iPSC as an alternative source for therapeutic cells and artificial organs for diseases in which human tissues or organs are inaccessible to investigate. Recognizing their discovery and productive market, Japan government amended the Pharmaceutical and Medical Device Act (PMDA) in Nov 2013 opening door for regenerative medicine products. Revised PMDA act accelerated the iPSC-based therapy development by set-



ting the fastest approval system for clinical trials in the world²⁸⁻³⁰. In Japan, therapeutic cells derived from iPSCs have been transplanted into wet-type AMD and Parkinson's disease, while more clinical studies are planned for other conditions. In recent years, the Japan government is setting to host world's first pre-trial clinical studies for several diseases and had approved physician-led clinical trials as listed in **Table 2**. The country's scientists are now leading the way with clinical translation.

It is obvious that the challenges encounter when closer to clinical trials, but that also leads to the process for scientific discovery. In 2013, Japan took credit for historical movement in the race to develop iPSC-based therapies and considered as a landmark year. A panel of Japan's Health Ministry approved the project

for autologous transplantation RPE sheets derived from iPSC in patients with wet-type AMD³⁹. The project was conducted at RIKEN Center in Kobe, Japan, which was led by Masayo Takahashi of the RIKEN Center for Developmental Biology (CDB). RIKEN is the largest national scientific research institute supported by Japan's Health Ministry and exclusively funded by the Japanese government^{40,41}. For the first patient enrolled, iPSC-derived RPE patch was transplanted in September 2014. One-year follow-up observation showed a good safety profile without significant improvement in visual acuity but stopped the progression of the disease⁴². However, transplant was halted in second patients due to genomic alteration in the patient's iPSC-derived RPE cells, owing to the possible risk of aberrations in DNA copy num-

Table 2: World's first iPSC-based pretrial clinical studies approved in Japan

iPSC Derivatives	Disease	Principal Investigators	Start of the Clinical Trials	References
Retinal Pigment Epithelium (RPE)	Wet-type age-related macular degeneration	Masayo Takahashi; RIKEN Center	12 Sep 2014 Transplanted	31
Dopaminergic Progenitors	Parkinson's Disease	Jun Takahashi; Kyoto University	Oct 2018 Transplanted	32
Cardiomyocytes	Severe Heart Disease	Yoshiki Sawa; Osaka University	16 May 2018 Approved	33
Platelets	Aplastic Anemia	Koji Eto; Kyoto University	21 Sep 2018 Approved	34
Neural Cells	Spinal Cord Injuries	Hideyuki Okano; Keio University	18 Feb 2019 Approved	35
Corneal Epithelium	Corneal Diseases	Koji Nishida; Osaka University	March 2019 Approved	36
Natural Killer T Cells	Head and neck Cancers	Haruhiko Koseki; RIKEN Center	11 Jan 2019 Planned	37
Candidate Drug (Rapamycin)	Fibrodysplasia Ossificans Progressiva	Junya Toguchida; Kyoto University	1 Aug 2017 Clinical Trial	38

bers (deletions)⁴². Surprisingly, new regulation was implemented in regenerative medicine legislation of Japan in November 2014 that state, “the proposal for pretrial clinical study should be submitted from medical but not research institutions”. Thus, patient enrollment was immediately halted for RPE cell therapy in 2015. Later in 2017, allogenic HLA-matched iPSC-derived RPE cells were transplanted in the second patient⁴³. Interestingly, Kyoto Hospital made an official announcement for establishment of special iPSC therapy center with 30-bed ward to conduct clinical studies for testing safety and efficacy of the iPSC therapies on volunteer patients. They aim to finish complete setup by September 2019 and planning to get approval for iPSC-based product by 2020.

Globalization of Japan iPSC and derivatives

iPSC-based therapies should be available to global population. Therefore, making availability of quality iPSC and derivatives become commercially important. To move forward with global clinical trials using iPSC-RPE for treatment of AMD, Healios K.K. established a patent license agreement with RIKEN in August 2011. They hold the exclusive worldwide license covering regenerative products that contain iPSC-derived RPE cells. Additionally, Healios establish collaboration with Sumitomo Dainippon Pharma for joint development of new therapies for wet-type AMD in Japan and also with National Eye Institute

(NEI) for dry-type AMD in US/EU^{44,45}. Next, Cynata Therapeutic in joint development with Japanese company, Fujifilm received approval from the U.K. and Australia government in September 2016, to begin a clinical trial using allogenic iPSC-derived mesenchymal stem cells (MSCs) for treating graft-versus-host disease (GVHD)⁴⁶. The world's first clinical trial of an allogeneic cell product, “CYP-001” derived from iPSC begins in both the U.K. and Australia⁴⁶. In this historic trial, Australian regenerative medicine company is testing product for GVHD⁴⁷. GVHD is a transplant complication, in which the donor's immune T cells (graft) attack the patient's healthy cells or tissues (host) and damage them. iPSCs-derived MSCs were implanted, and two years post-implantation data from all 16 participants are expected to be completed by May 2020 to evaluate the safety and efficacy.

Japan iPSC banking and online database for global population

Patient-specific iPSCs are becoming challenging due to time-consuming to generate iPSC derivatives from patient somatic cells⁴⁸, and chance of carrying somatic mutation into iPSCs⁴⁹. Such challenges pose risk for missing threshold time for transplantation and effects of mutation inherited from parental cells. So, there is prerequisite of healthy donor for reducing the cost and rapid availability for cell therapy to the patients. To overcome the need of autologous cell

therapy or immune rejection associated with human leucocytes antigen (HLA) mismatch⁵⁰, CiRA is establishing the iPSC stock for medical use by recruiting the HLA homozygous (HLA-A, -B, and -D.R.) super donors. iPSCs derived from super donor somatic cells reduced the risk of rejection when transplanted in patient with heterozygous HLA for same haplotypes⁵¹. Currently they have 4 HLA homozygous iPSC lines, which cover 40% of Japan's population. In addition, using genome editing technology, they estimated to generate 10-12 iPSC lines that will cover more than 90% of world population. "My iPSC cells" project is next in the line to begin from 2025 as disclosed by Yamanaka during his presentation at ISSCR 2019 annual meeting held between 26-29 June 2019 at Los Angeles, US. Interestingly, Akitsu and his colleagues generated HLA-C retained iPSCs by allele-specific genome editing to make immune compatible iPSC that will benefit to most of the global population. First HLA class I pseudo-homozygous iPSCs were generated from HLA heterozygous donors. Then, both allele of HLA-A and HLA-B and mono allele of HLA-C were deleted to retain one HLA-C allele to generated HLA-C retained iPSCs which greatly expand donor compatibility with larger populations⁵². Furthermore, with increase in number for iPSC research in global scenario, several iPSC online databases, such as eagle-I⁵³, hPSC^{reg}⁵⁴, RIKEN BRC⁵⁵, SKIP⁵⁶ were established. Recently, CiRA professor Wataru Fujibuchi combined all those databases and released Integrated Collection of Stem Cell Bank Data (ICSCB) by MIACARM (Minimum Information About a Cellular Assay for Regenerative Medicine)⁵⁷. ICSCB database provides the uniform, accurate and user-friendly data exchange that will facilitate the accelerated access to iPSCs data for research.

CONCLUSIONS

iPSCs are promising platform for future medicine, such as cell-based therapy for reversing diseases, patient specific-iPSC biobanking to investigate a diverse range of conditions, use of physiologically relevant cells derived from iPSC for drug development & discovery, and iPSC-derivatives for toxicology screening. Because, iPSC was discovered by the Japanese scientist, the country's researchers working in the field of regenerative medicine consider iPSCs as promising sources for therapeutic cells. Also, the government of Japan supports for the iPSC research, amended the regenerative medicine law for fast approval system for pretrial clinical studies and commercialization of iPSC-related products by holding basic patent licensing from most of the countries. To conclude, the iPSC

is a brand source of Japan that provide clinical grade iPSC and related products worldwide. Also, Japan-based companies were investing massive funds in the iPSC-based research and collaborated with multinational companies globally to promote the use of iPSC for clinical trials.

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Due to space limitations, I had to limit the number of citations. I apologize to those authors whose work has not been cited here.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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