Confidential

Introduction and Notes of iPS Cell Stock

As of 2024/01/19

CiRA Foundation

公益財団法人
京都大学iPS細胞研究財団

Contents

CiRA Foundation

April 1, 2020
Registered as a public interest incorporated Foundation by the Cabinet Office
(Located inside CiRA buildings)

Center for iPS Cell Research and Application
Kyoto University

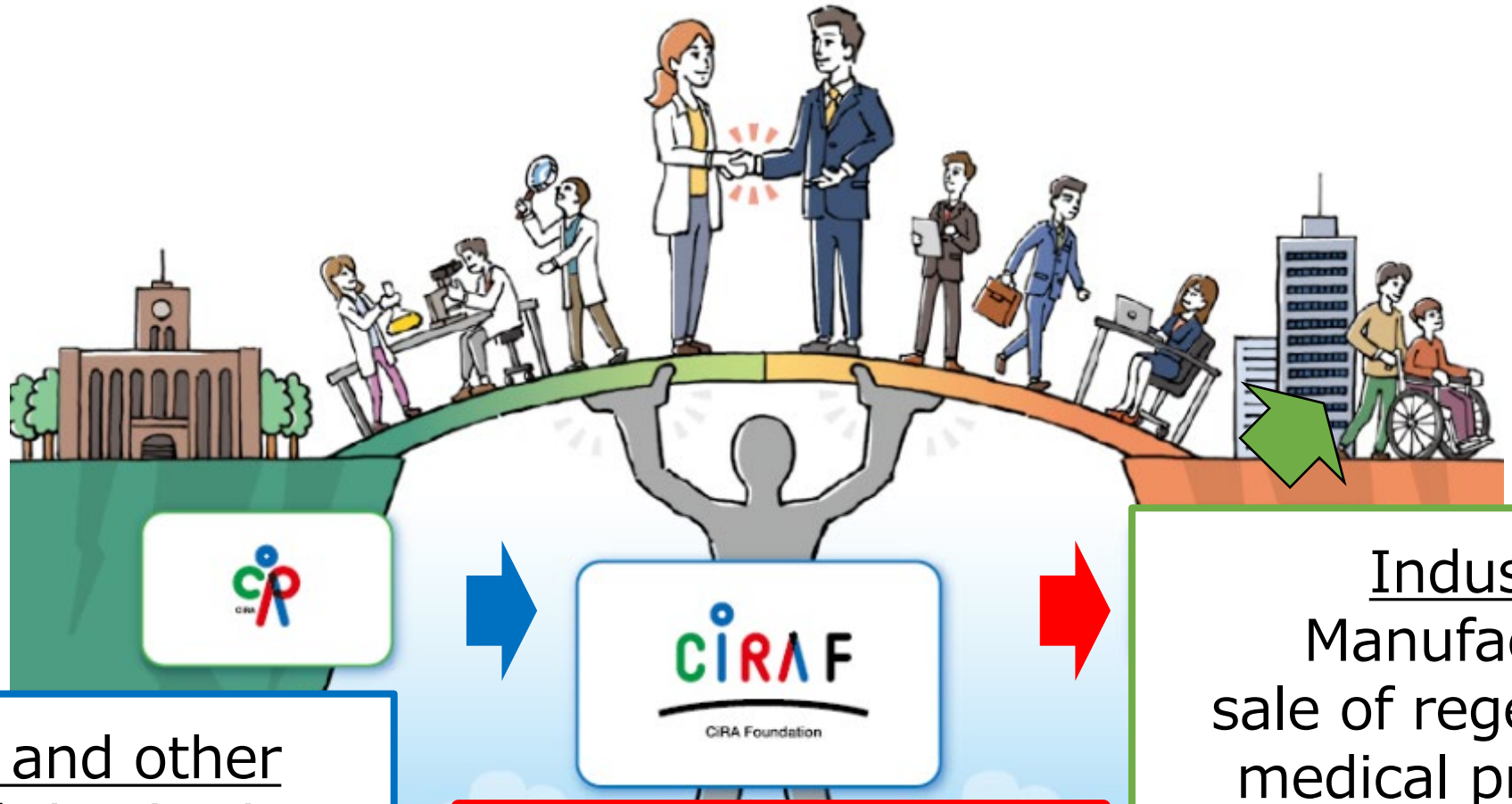
CiRA

- **Basic Research**
- **Medical Application**
- **Education Training**
- **iPSCs Manufacturing, QC and Storage**





Our purpose：Bridge over the valley of death



<u>CiRA and other research institutions</u>
Basic research on iPSCs

<u>CiRA Foundation</u>
Manufacturing iPSCs, Bridge to industry

<u>Industry</u>
Manufacture, sale of regenerative medical products/ Provision to medical institutions

Facility for iPS Cell Therapy (FiT)

■ License

We obtained the manufacturing license based on the PMD Act. (License#26FZ110001)

*We are also recognized as the Cell Processing Center.
(the Japan Act on Securement of Safety of Regenerative Medicine)
(Facility#FA5200001)

■ Experience

Abundant experience in the production/testing of clinical grade iPSCs and iPSC-derived differentiated cells under the GMP-compliant quality system and facilities.

Our iPS Cell lines

■ iPS Cell Stock

We have been providing off-the-shelves **clinical-grade iPSCs** at low cost since 2015.

HLA-homozygous iPSCs

These iPS cells were generated from the blood of healthy donors who are homozygous in their expression of the protein HLA-A, HLA-B, or HLA-DR. We provide 27 clinical-grade cell lines from 7 donors and some of these cell lines were used in several Japanese clinical trials/research.

HLA-genome-edited iPSCs

These iPS cells are designed to reduce the risk of immune rejection. We manufacture and provide them by targeting HLA-A, -B, and -CIITA for the genome-edited knockout. Also, they are capable of suppressing both T and NK cell activity because they retain HLA-C and HLA-E.

SeV-iPSCs

These iPS cells were made using Sendai Virus (SeV) vectors, instead of Episomal Plasmids. From a patent licensing point of view, we recommend them to commercial users.

■ Research Materials

We provide human-derived research materials. Users can use them even for **drug discovery**, but we don't provide clinical-grade ones for regenerative medicines.

CFiS Series

These are research-grade iPS cells generated from the blood of a healthy donor who isn't homozygous in HLA. Users can use them just by agreeing with the terms and conditions.

Covid-19 iPSCs

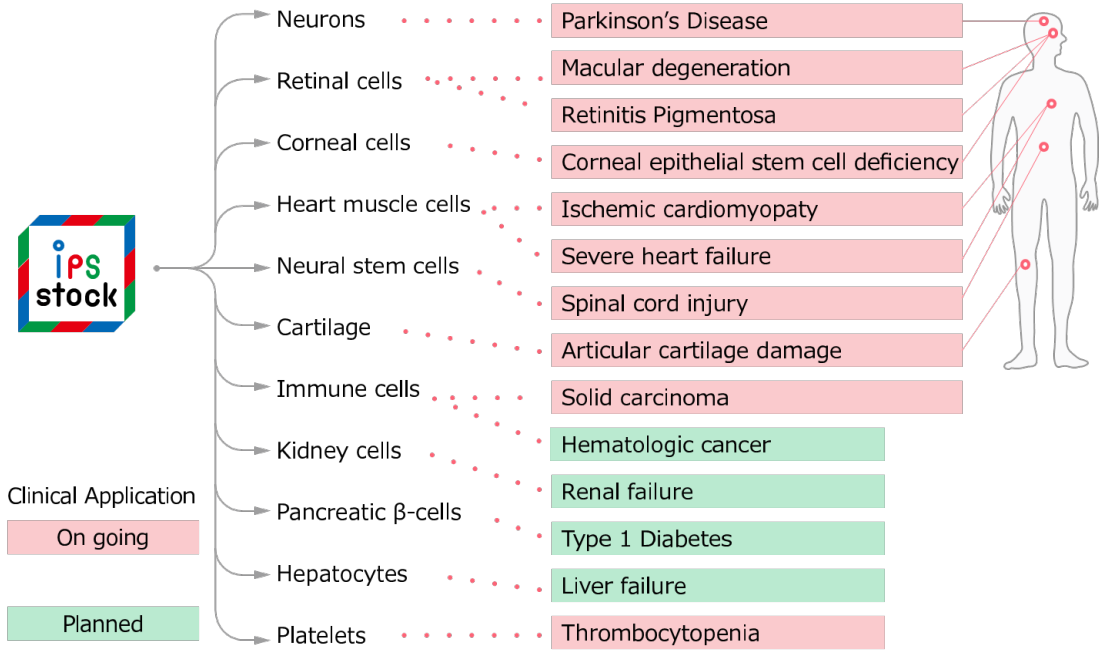
These iPS cells were made from COVID-19 convalescent patients.

What is iPS Cell Stock?

“iPS Cell Stock” is a high-quality off-the-shelf iPSC for regenerative medicine.

high-quality

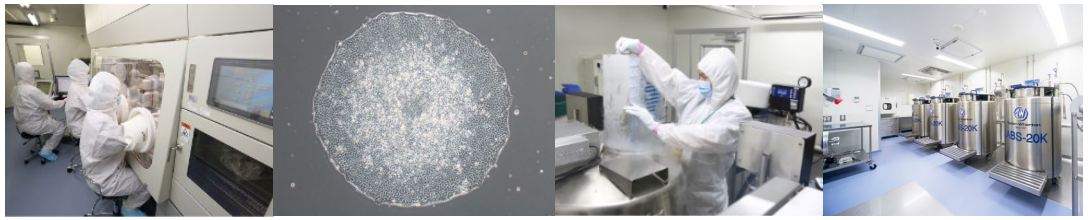
Already used in several Japanese clinical trials!



off-the-shelf

Able to choose iPSCs from several cell lines!

- **HLA-homozygous iPSCs**
  27 clinical-grade lines from **7** donors
- **HLA-genome-edited iPSCs**
  2 clinical-grade lines from **1** donor
- **SeV-iPSCs**
  2 clinical-grade lines from **1** donor



Precautions

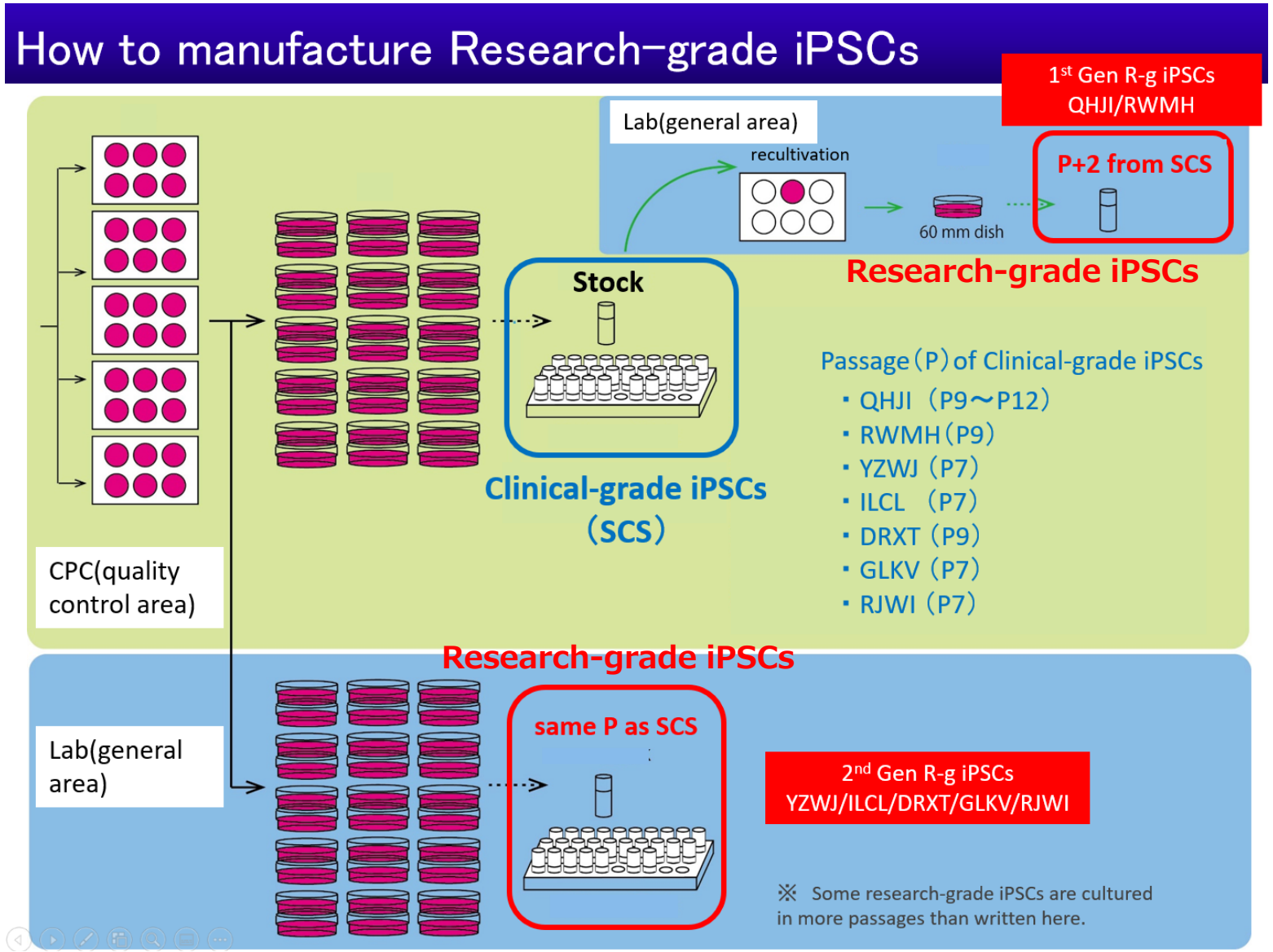
1. If users want to utilize clinical-grade iPSCs, we kindly request that users first use our research-grade iPSCs and share with us the results of differentiation, such as immunostaining figures. Due to the limited availability of vials for our clinical-grade iPSCs, we primarily offer them to users who have previously utilized our iPSCs. But as for these cell lines (KTRH05, KTRH26, QHJI14s04-ABⅡ-KO-03, and QHJI14s04-ABⅡ-KO-11), users can first use clinical-grade iPSCs.

2. We only provide our iPSCs to institutions or companies with research plans that appropriately comply with local regulations, such as IRB approvals.

3. Users should get the appropriate license from iPS Academia Japan which controls the patents of iPS Cells. For further details and inquiries, please directly engage with iPS Academia Japan. The third-party patent information will be provided during the contract signing process. At their own risk, users may need to refer to and deal with effective patents in their country.

4. We acknowledge that users shall have exclusive ownership of differentiated cells, but please note that ownership of iPSCs doesn’t transfer to users. If users need to get ownership of iPSCs, they have to sign the ownership transfer agreement. After signing it, we’ll transfer the ownership with non-transferable covenants.

What is Research-grade iPSCs?

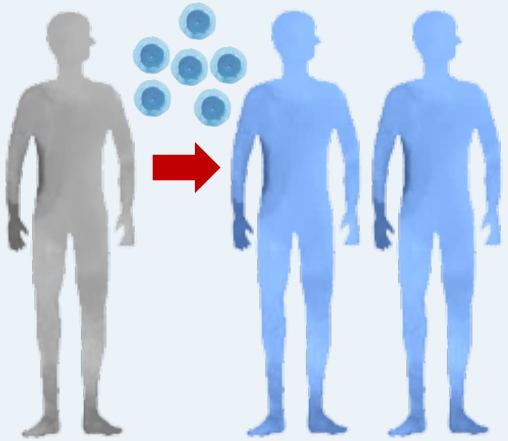


3 strategies to promote iPSC therapy

Allogenic iPSC

HLA-homozygous

Super donor → Patient

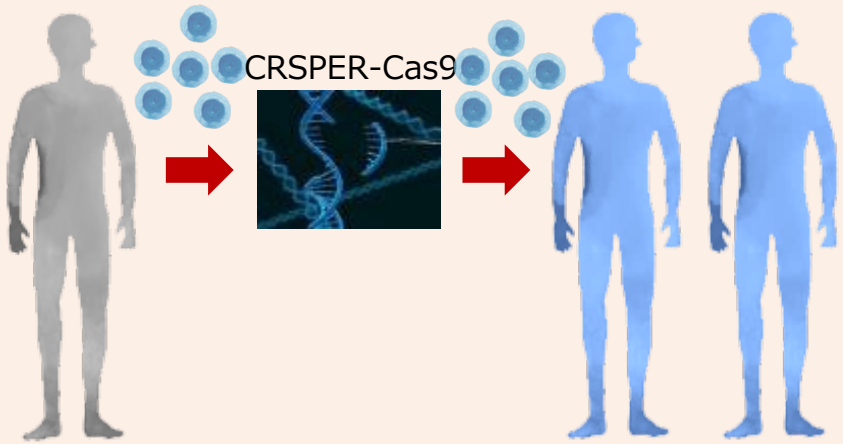


27 cell lines / 7 donors

Cover ca.40% of Japanese

HLA-genome-edited

Super donor → CRSPER-Cas9 → Patient

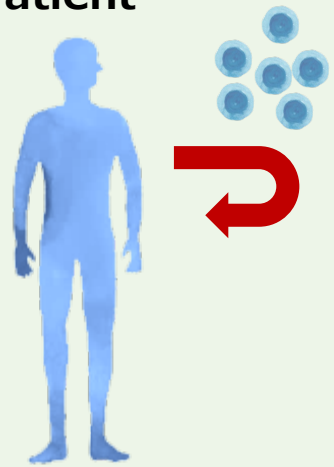


HLA-A, HLA-B, CⅡTA edited

Worldwide coverage

Autologous iPSC

Patient



my iPS®

Order made

Progress in our iPSC-based cell therapy

Sponsor/Investigator	iPS cell line	Cell type	Disease indications	Current stage
Masayo Takahashi (RIKEN)	QHJI01s04	Retinal pigment epithelium (cell suspension)	Age-related macular degeneration	Clinical Research：Completed
		Photoreceptor cells (Neural retinal sheet)	Retinitis pigmentosa	Clinical Research：Completed
Masayo Takahashi (Kobe City Eye Hospital)	QHJI01s04	Retinal pigment epithelium (cell suspension)	RPE impaired disease	Clinical Research: Terminated
		Retinal pigment epithelium (cell strips)	RPE impaired disease	Clinical Research：Recruiting
Yasuhiko Hirami (Kobe City Eye Hospital)	QHJI01s04	retinal sheets	Retinitis pigmentosa	Clinical Research：Active, not recruiting
Jun Takahashi (Kyoto University)	QHJI01s04	Dopaminergic progenitor cells (cell aggregate)	Parkinson's disease	Clinical Trial：Active, not recruiting
Yoshiki Sawa (Osaka University Graduate School of Medicine)	QHJI14s04	Cardiomyocytes (Cell patch)	Ischemic Cardiomyopathy	Clinical Trial：Recruiting
Hideyuki Okano (Keio University School of Medicine)	YZWJs513	neural stem/progenitor cells (cell suspension)	Spinal cord injury at subacute stage	Clinical Research：Recruiting
Kohji Nishida (Osaka University Graduate School of Medicine)	YZWJs524	Corneal epithelium (allogeneic, cell sheet)	Corneal opacity due to limbal stem cell deficiency	Clinical Research：Completed
Noriyuki Tsumaki (Kyoto University)	QHJI01s04	Chondrocytes (Cartilage tissue)	Knee articular cartilage damage	Clinical Research：Active, not recruiting
Keiichi Fukuda (Keio University School of Medicine)	QHJI14s04	Ventricular cardiomyocytes (Spheres)	Heart failure (Dilated cardiomyopathy)	Clinical Research：Recruiting
Heartseed Inc.	QHJI14s04	Ventricular cardiomyocytes (Spheres)	Heart failure (Ischemich heart disease)	Clinical Trial：Recruiting
Shin Kaneko (Kyoto University)	QHJI01s04	Innate lymphoid cells (Natural Killer Cells)	Ovarian cancer	Clinical Trial：Recruiting
Megakaryon Co.	YZWJs513	Platelets	Thrombocytopenia	Clinical Trial：Recruiting
Shigeto Shimmura (Keio University School of Medicine)	QHJI01s04	Corneal endothelial cell (cell suspension)	Bullous keratopathy	Clinical Research：Recruiting

Modified Table.3 in a paper by Yoshida et al., *Med* (2022) DOI：10.1016/j.medj.2022.10.003

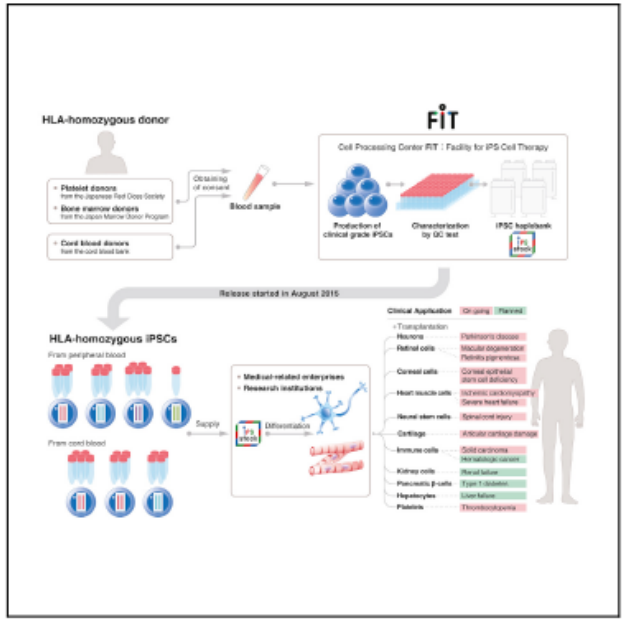
Paper on iPSC Stock

Med

CellPress
OPEN ACCESS

Clinical and Translational Resource and Technology Insights

A clinical-grade HLA haplobank of human induced pluripotent stem cells matching approximately 40% of the Japanese population



Producing haplobanks of human iPSC lines from HLA-homozygous donors is a potentially cost- and time-effective strategy to match large populations. Here, Yoshida et al. construct a clinical-grade haplobank of 27 iPSC lines matching 40% of the Japanese population, which have already been used in more than 10 clinical trials.

Shinsuke Yoshida, Tomoaki M. Kato, Yoshiko Sato, ..., Masayoshi Tsukahara, Naoko Takasu, Shinya Yamanaka

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yamanaka@cira.kyoto-u.ac.jp (S.Y.)

Highlights

A clinical-grade iPSC haplobank was established from seven HLA-homozygous donors

After screening and release tests, 27 iPSC lines were selected for clinical usage

Pluripotency of iPSC lines was confirmed *in vitro*

The established iPSC haplobank has been used in more than 10 clinical trials

Table 3. Progress in iPSC stock-based cell therapy

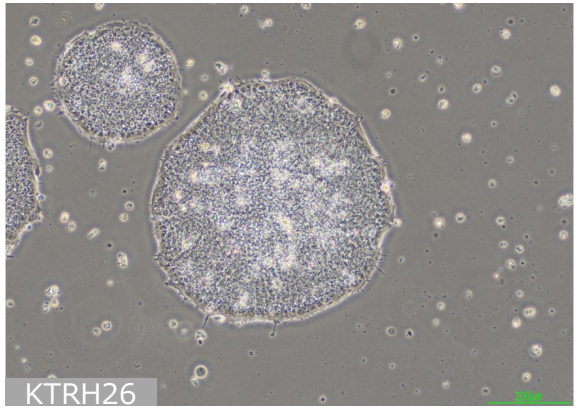
Sponsor/investigator	iPSC line	Cell type	Disease indications	Current stage	Reference
Masayo Takahashi (RIKEN)	QHJI01s04	retinal pigment epithelium (cell suspension)	age-related macular degeneration	clinical research[a]: completed	Sugita et al.[20,21]
Masayo Takahashi (Kobe City Eye Hospital)	QHJI01s04	retinal pigment epithelium (cell suspension)	RPE impaired disease	clinical research: terminated	Maeda et al.[22]
		retinal pigment epithelium (cell strips)	RPE impaired disease	clinical research: recruiting	Nishida et al.[23]
Yasuhiko Hirami (Kobe City Eye Hospital)	QHJI01s04	retinal sheets[b] (retinal tissue containing photoreceptors)	retinitis pigmentosa[b]	clinical research[b]: active, not recruiting	Tu et al.;[24] Kuwahara et al.[25]
Jun Takahashi (Kyoto University)	QHJI01s04	dopaminergic progenitor cells[c] (cell aggregate)	Parkinson's disease[c]	clinical trial[c]: active, not recruiting	Kikuchi et al.;[26] Takahashi;[27] Doi et al.[28]
Yoshiki Sawa (Osaka University Graduate School of Medicine)	QHJI14s04	cardiomyocytes (Cell patch)	ischemic cardiomyopathy	clinical trial: recruiting[d]	Kawamura et al.;[29] Kashiyama et al;[30] Ito et al.[31]
Hideyuki Okano (Keio University School of Medicine)	YZWJs513	neural stem/progenitor cells (cell suspension)	spinal cord injury at subacute stage	clinical research: recruiting	Nakamura and Okano;[32] Sugai et al.[33]
Kohji Nishida (Osaka University Graduate School of Medicine)	YZWJs524	corneal epithelium (allogeneic, cell sheet)	corneal opacity due to limbal stem cell deficiency	clinical research: completed	Hayashi and Nishida et al.[34, 35]
Noriyuki Tsumaki (Kyoto University)	QHJI01s04	chondrocytes (cartilage tissue)	knee articular cartilage damage	clinical research: active, not recruiting	Takei et al.;[36] Chen et al.;[37] Yamashita et al.[38]
Keiichi Fukuda (Keio University School of Medicine)	QHJI14s04	ventricular cardiomyocytes (spheres)	heart failure (dilated cardiomyopathy)	clinical research: recruiting	Hattori et al.;[39] Tohyama et al.[40,41]
Heartseed	QHJI14s04	ventricular cardiomyocytes (spheres)	heart failure (ischemic heart disease)	clinical trial: recruiting[e]	Hattori et al.;[39] Tohyama et al.[40,41]
Shin Kaneko (Kyoto University)	QHJI01s04	innate lymphoid cells (natural killer cells)	ovarian cancer	clinical trial: recruiting	Ueda et al.[42]
Megakaryon	YZWJs513	platelets	Thrombocytopenia	clinical trial: recruiting	Ito and Nakamura et al.[43]
Shigeto Shimmura (Keio University School of Medicine)	QHJI01s04	corneal endothelial cell (cell suspension)	bullous keratopathy	clinical research: recruiting	Hatou et al.[44]

Yoshida et al., *Med* (2022)
DOI : 10.1016/j.medj.2022.10.003

Available cell lines: KTRH series

1）US donor-derived iPS Cells with Sendai virus vector

Grade	Clinical-grade	Research-grade
Cell lines	KTRH05 KTRH26	*Users can use clinical-grade cell lines for research use.



Source	Human peripheral blood, derived from healthy US donor
Vector	Sendai Virus vectors（CytoTune®）
Feature	✓ Conformable to the donor eligibility regulations of Japan, the U.S., and Europe. ✓ We used the Sendai virus vector instead of episomal plasmids. （No residuals of the Sendai virus confirmed.） ✓ Users can use clinical-graded cell lines even if it is the first provision.
Provision Fee	To non-profit: **Free**　To profit: **JPY100,000 /one vial** (~USD690, 1USD=145JPY)
Notice	Homozygous only in HLA-A

Available cell lines: QHJI series

2) Most used HLA-homozygous iPS Cells derived from PBMC

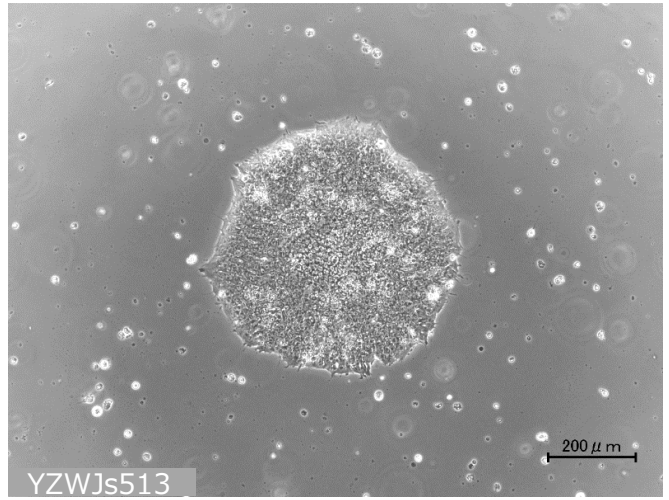
Grade	Clinical-grade	Research-grade
Cell lines	QHJI01s04 QHJI14s03 QHJI14s04	Ff-I01s04 Ff-I14s03 Ff-I14s04

Source	Human peripheral blood, derived from healthy Asian donor
Vector	Episomal Plasmids
Feature	✓ The underlined cell lines were used in several Japanese clinical trials/research. (Please refer to our paper "Yoshida et al., Med (2022)DOI：10.1016/j.medj.2022.10.003".)
Provision Fee	To non-profit: **Free** To profit: **JPY100,000 /one vial** (~USD690, 1USD=145JPY)
Notice	Homozygous in HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ and HLA-DP

Available cell lines: YZWJ series

3) Most used HLA-homozygous iPS Cells derived from Cord Blood

Grade	Clinical-grade	Research-grade
Cell lines	YZWJs513 YZWJs516 YZWJs524 YZWJs527 YZWJs531	Ff-WJs513 Ff-WJs516 Ff-WJs524 Ff-WJs527 Ff-WJs531



Source	Human umbilical cord blood, derived from healthy Asian donor
Vector	Episomal Plasmids
Feature	✓ The underlined cell lines were used in several Japanese clinical trials/research. (Please refer to our paper "Yoshida et al., Med (2022)DOI：10.1016/j.medj.2022.10.003".)
Provision Fee	To non-profit: **Free** To profit: **JPY100,000 /one vial** (~USD690, 1USD=145JPY)
Notice	Homozygous in HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ and HLA-DP

List of available cell lines

Derived from **PBMC** HLA: Homozygous (HLA-A-B-DRB1) Vector: Episomal Plasmid	**Clinical-grade**	**Research-grade**
Donor: QHJI (24:02-52:01-15:02)	QHJI01s01 *Genomic mutations in BCOR and BRD3 genes were detected in this clone.	Ff-I01s01
	QHJI01s04	Ff-I01s04
	QHJI14s03	Ff-I14s03
	QHJI14s04	Ff-I14s04
Donor: RWMH (33:03–44:03–13:02)	RWMH09s01	Ff-MH09s01
	RWMH15s01	Ff-MH15s01
	RWMH15s02	Ff-MH15s02
	RWMH23s01	Ff-MH23s01
Donor: DRXT (24:02–07:02–01:01)	DRXT18s02	Ff-XT18s02
	DRXT18s03	Ff-XT18s03
	DRXT28s04	Ff-XT28s04
	DRXT28s05	Ff-XT28s05
	DRXT28s17	Ff-XT28s17
Donor: RJWI (24:02–54:01–04:05)	RJWIs03	Ff-WIs03

List of available cell lines

Derived from **Cord Blood** HLA: Homozygous (HLA-A-B-DRB1) Vector: Episomal Plasmid	**Clinical-grade**	**Research-grade**
Donor: YZWJ (24:02–52:01–15:02)	YZWJs513	Ff-WJs513
	YZWJs516	Ff-WJs516
	YZWJs524	Ff-WJs524
	YZWJs527	Ff-WJs527
	YZWJs531	Ff-WJs531
Donor: ILCL (24:02–52:01–15:02)	ILCLs14	Ff-CLs14
	ILCLs21	Ff-CLs21
	ILCLs23	Ff-CLs23
	ILCLs31	Ff-CLs31
Donor: GLKV (33:03–44:03–13:02)	GLKVs09	Ff-KVs09
	GLKVs13	Ff-KVs13
	GLKVs16	Ff-KVs16
	GLKVs31	Ff-KVs31

List of available cell lines

Derived from PBMC Vector: **Sendai Virus**	**Clinical-grade**	**Research-grade**
Donor: KTRH	KTRH05	*Users can use clinical-graded cell lines for research use.
	KTRH26	

List of available cell lines

HLA: **Genome-edited** with CRISPR-Cas9 Vector: Episomal Plasmid	**Clinical-grade**	**Research-grade**
Derived from QHJI14s04	QHJI14s04/AB Ⅱ-KO-03	*Users can use clinical-graded cell lines for research use.
	QHJI14s04/AB Ⅱ-KO-11	
	QHJI14s04/AB Ⅱ-KO-12	

HLA: **Genome-edited** with CRISPR-Cas9 Vector: Episomal Plasmid	**Research-grade**
Derived from Ff-I01s04	Ff-I01s04-AB II-KO-16
	Ff-I01s04-AB II-KO-50
	Ff-I01s04-AB II-KO-54
Derived from Ff-I14s04	Ff-I14s04-AB II-KO-7
	Ff-I14s04-AB II-KO-13
	Ff-I14s04-AB II-KO-24
Derived from Ff-XT28s05 *Not established by CiRA_F	Ff-XT28s05-cont *This cell line is not genome-edited because it's for control use.
	Ff-XT28s05-ABo_To

Kitano et al., Molecular Therapy - Methods & Clinical Development 26 15-25 (2022): https://doi.org/10.1016/j.omtm.2022.05.010

Provision Fee (Up-front Payment per vial)

iPS Cell Stock	To Non-Profit (ex. university, research institution)	To Profit (ex. private company, start-up)
HLA homozygous		
-Research-grade :	Free	JPY 50,000/one(1) vial
-Clinical-grade :	Free	JPY 100,000/one(1) vial
SeV iPS /"KTRH"		
-Only Clinical-grade :	Free	JPY 100,000/one(1) vial
HLA genome-edited		
-Research-grade :	Free	JPY 100,000/one(1) vial
-Clinical-grade :	Free	JPY 200,000/one(1) vial

- ✓ In addition to the provision fee above, an applicant of iPSC stock, whether profit or non-profit, is required to arrange for shipping from CiRA Foundation to its research location by its cost.
- ✓ After obtaining market authorization for the product, the applicant will owe iPS Stock System Maintenance Fee (Please see the next slide).
- ✓ We provide only research-grade iPS Cell stock to new users who first use our iPS Cell Stock in principle. But as for HLA genome-edited lines and KTRH lines, users can use clinical-grade iPS Cell Stock for their non-clinical research.

Procedure for using the iPSC stock

1 User Registration

A few days

✓ New users only

2 Application

1 month

✓ Per each research plan

3 Examination of Application by iPS Cell Stock Review Committee

1 month

4 Agreement

A few weeks

✓ Collaborative research agreement with CiRA foundation
✓ License agreement with iPS Academia Japan: commercial organizations only

5 Shipping iPS Cells and Payment

Please see our website for details.
https://www.cira-foundation.or.jp/e/project/stock.html

Required documents for a new application

	Required documents	Notes
Before you apply	(Form0) iPS Cell Stock New Application Confirmation Request Form	We upload the blank form of this document. Please refer to the website below. https://www.cira-foundation.or.jp/e/research-institution/ips-stock-project/stock.html
When you apply	New application / Change application	You can submit them by our application system.
	Research Plan ※	Please prepare a research protocol that has been or will be submitted to an ethics review committee, etc. (For research conducted outside of Japan) If a review by an Ethics Review Committee is not required, please prepare a sheet of A4-sized research outline that includes the following information at a minimum, with 300-500 words. ・Target Disease(s) ・Type of differentiated cells ・Milestones or Aims of the research plan
	Letter of ethical approval ※	Please prepare the ethical approval letter for your research proposal. (For research conducted outside of Japan) If a review by an Ethics Review Committee is not required, please prepare a notification or an email from the Ethics Review Committee that shows it's not required.
	Documentation on how to store each grade of cell obtained ※	Please prepare a file that describes the management system in your organization for the iPS cell stock you plan to be provided by us. Please refer to this template. (Reference -low to store provi
	（Only if you first use our iPS Cell Stock）※ ・Biography of the principal researcher ・Overview of the institution ・Materials on the research performance	Please attach papers or other materials(posters or data in differentiation such as flow cytometry) that include the following information. If the material is divided into multiple documents, please also upload them in the "Other references" section. ・Experience in culturing human iPS cells ・Experience in inducing differentiation into target cells from human iPS Cells

※ If you have partner institutions which use our iPSCs together, please prepare their documents too.

Contact us

■ About iPS Cell Stock

ips-stock-shinsa*cira-foundation.or.jp
Please change * to @

■ About Research Materials

minnano-saibou*cira-foundation.or.jp
Please change * to @

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