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Korea National Stem Cell Bank

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A B S T R A C T

The Korea National Stem Cell Bank has been banking pluripotent stem cell (PSC) lines since 2012. Quality-controlled and ethically sourced cell lines were developed for distribution. Currently (as of 2020), among the 69 deposited lines, 4 research-grade human embryonic stem cell (hESC) lines and 19 induced pluripotent stem cell (iPSC) lines have been distributed. Good manufacturing practices (GMP)-compliant homozygous iPSC lines for regenerative medicine with homozygous HLA haplotypes that cover 51% of the Korean population have been deposited as well. To ensure the quality of the cell lines, we performed eighteen different quality tests on the identity, sterility, consistency, stability and safety of the cell lines. Regarding genetic stability, we are collecting SNPchip, WES, Methyl-seq, and RNA-seq data, which are open to the public.

1. Introduction

The Korea National Stem Cell Bank (KSCB) is administered under the Korea National Institute of Health (KNIH) as one of the infrastructures to provide easily accessible stem cell resources and regenerative medicine information. The major activities of the KSCB are human embryonic stem cell (hESC) registration, national stem cell banking and Good Manufacturing Practice (GMP) facility services as a contract-based manufacturing organization (CMO) for cell therapy products.

2. Human embryonic stem cell registry

The application of hESCs needs to be ethical and safe. Therefore, research applications related to hESC lines were enacted by the Bioethics and Safety Act in Korea. The Ministry of health and welfare approves research proposals that establish hESC lines from residual embryos. The KSCB registers the resulting hESC lines through confirmation of scientific characteristics and documents for informed consents. As of 2020, 106 hESC lines established in Korea and 41 hESC lines imported from abroad are included in our registry.

3. Pluripotent stem cell banking

The Korea National Stem Cell Bank is the national stem cell repository. Sixty-nine hPSC lines, 17 tissue-derived adult stem cells and 228 genetic disease primary cells have been deposited for research use. Currently, 4 hESC lines and 19 iPSC lines are being distributed (Table 1). In addition to the research lines, we have also deposited 22 GMP-compliant homozygous HLA-type iPSC lines, which cover HLA haplotype matching for 51% of the Korean population. For these clinical-grade iPSC lines, we have research-grade stocks that are available. GMP-grade lines will be released to the public beginning next year. To reduce the cell passage number, we follow the International Stem Cell Banking Initiative recommendation of three-step banking: pre-master, master and distribution steps (Andrews, 2015). The cell lines were distributed to 266 laboratories within Korea from 2014 to 2020. We provide frozen vials without fees. For domestic users, we do not ship the cells; rather, we recommend picking up frozen vials. For international distribution, we are currently preparing a standard distribution process.

4. Quality control of the banked lines

4.1. Research lines

Compliance with quality control (QC) standards is a critical requirement for banked products (Kim, 2017, 2019). We are performing 18 different tests (Table 2) that can be used to determine the identity (STR, parental cell STR, HLA, parental cell HLA, parental cell ABO, and ABO), sterility (mycoplasma, viral testing, fungi testing, bacteriology testing, and endotoxin testing) viability (cell counting), Pluripotency (morphology, AP staining, EB formation, and teratoma formation), stem cell markers (immunocytochemistry and real-time PCR), abd stability (karyotype, CNV, SNPchip) of the cell lines to ensure quality (Table 2). The QC data on the cell line are provided with the frozen vial and cell

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line characteristics are available online (nih.go.kr/contents. Es?mid = a40405011000).

4.2. GMP-compliant iPSC lines

Quality control of GMP-compliant iPSC lines is a critical step for ensuring the safety of the product (Jo, 2020). In GMP-compliant iPSC line manufacturing, we follow the minimum safety requirements for releasing iPSC stocks according to the Korea MFDS guidelines (Table 2).

5. Genetic stability of the banking lines

5.1. Genetic testing

We routinely detect copy number variations (CNVs) based on a SNP array to ensure the genetic stability of hPSCs distributed from the KSCB. We established CNV pipelines to detect recurrent and novel CNVs that can cause functional consequences (Jo, 2020). In addition, to leverage genetic quality control criteria and further the genomic studies of hPSCs for distribution, genomic data of hPSCs, including whole-exome sequencing (WES), RNA sequencing (RNA-seq), and targeted bisulfite sequencing data, have been accumulated.

6. Data availability

The genomic data, including raw and processed data, have been deposited in the NCBI GEO database under accession number GSE163134 for the SNP array, and NCBI SRA under project number PRJNA685393 for WES, RNA-seq, targeted bisulfite sequencing (Table 2). The cell lines' significant CNV data are also available through the Korea National Stem Cell Bank Institute website (http://kscr.nih.go.kr).

Table 2
Releasing QC test regimens.

	Research-grade iPSC stocks	GMP-compliant iPSC stocks
Identity	STR	STR
	HLA	HLA
	ABO	ABO
Purity	–	Residual viral OSKM gene silencing
Sterility	Mycoplasma (PCR)	Mycoplasma (Agar and Broth assays)
	Viral	Viral
	Fungi	Fungi
	Bacterial	Bacterial
	Endotoxin	Endotoxin test
	–	Adventitious viruses test
Viability	Cell counting	Cell counting
		Viable cell counting
Pluripotency	Morphology	Morphology
	AP staining	–
	Pluripotent marker expression	Pluripotent marker expression
	EB formation	EB formation
	Teratoma formation	–
Stability	Karyotype	Karyotype
	CNV	CNV

*GMP-compliant iPSC stock donor eligibility testing is performed in the donor selection step.

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Table 1
Distributed lines and genomic data availability.

Cell Type	Cell Line	Passage for distribution	Passage for NGS data	Banking year	Origin	Culture	SNPchip	WES	RNA-seq	Methyl-seq
hESC	SNUhES3									
	SNUhES4									
	SNUhES31	p32	p34	2014		Matrigel	O	O	O (n = 2)	O
	CHA-hES15	p25	p28	2016		Matrigel	O	O	O	O
hiPSC	KSCBi002-B (hFmiPS1)	p26	p30	2014	Fibroblast	Matrigel	O	O	O (n = 2)	O
	KSCBi002-A (hFSiPS1)	p32	p34	2014	Fibroblast	Matrigel	O	O	O (n = 2)	O
	KSCBi002-B-1 (hFmiPS2)	p27	p27	2015	Fibroblast	Matrigel	O	O	O	O
	KSCBi001-A (hUSiPS2)	p24	p25	2015	Fibroblast	Matrigel	O	O	O	O
	NCRM5AS1-iCAGcGFP.c9	p74	p70	2015	CD34+ Cord Blood	Matrigel	O	O	O	O
	KSCBi005-A (CMC-hiPSC-003)	p18	p18	2017	Cord Blood	Vitronectin	O	O	O	O
	KSCBi0016-A (CMC-hiPSC-005)	p20	p20	2017	Cord Blood	Vitronectin	O	O	O	O
	KSCBi0017-A (CMC-hiPSC-009)	p27	p26	2017	Cord Blood	Vitronectin	O	O	O	O
	KSCBi0018-A (CMC-hiPSC-011)	p26	p26	2017	Cord Blood	Vitronectin	O	O	O	O
	KSCBi003-A (hAdMSiPS1)	p16	p18	2018	Adipocyte	STO	O	X	X	X
	KSCBi010-A (DHK-005iA)	p10	p6	2018	PBMC	Vitronectin	O	X	X	X
	KSCBi011-A (DHK-090iA)	p10	p6	2018	PBMC	Vitronectin	O	X	X	X
	KSCBi005-A-1(CMC-003i-Nestin.EGFP)	p14	p10	2018	Cord Blood	Vitronectin	O	X	X	X
	KSCBi005-A-3(CMC-003i-Pdx1.EGFP)	p18	p13	2018	Cord Blood	Vitronectin	O	X	X	X
	KSCBi0019-A (CMC-hiPSC-022)	p19	p19	2019	Cord Blood	Vitronectin	O	O	O	O
	KSCBi002-A-1(hFSiPS3-1)	p29	p30	2019	Fibroblast	Vitronectin	O	O	O	O
	KSCBi012-A (NU01-EiPS07)	p15	p13	2019	Urine	Vitronectin	O	X	X	X
	KSCBi013-A (PB01-EiPS21)	p18	p21	2019	PBMC	STO	O	X	X	X

*Cell line's standard nomenclature follows hESCreg (in-house naming) (Kurtz, 2018).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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