ANTICANCER RESEARCH *37*: 3367-3377 (2017)
doi:10.21873/anticanres.11703

Review

Application of Cancer Cell Reprogramming Technology to Human Cancer Research

XIU-YANG PAN[1], MING-HO TSAI[2], KENLY WUPUTRA[2], CHIA-CHEN KU[2], WEN-HSIN LIN[2], YING-CHU LIN[3], SHOTARO KISHIKAWA[4], MICHIYA NOGUCHI[4], SHIGEO SAITO[5], CHANG-SHEN LIN[2,6] and KAZUNARI K. YOKOYAMA[2,7-11]

[1]*Denyang and Qingxi Community, Qiushi College, Zhejian University, Hanzhou, P.R. China;*
[2]*Graduate Institute of Medicine,*[7]*Center of Stem Cell Research,* [8]*Center of Infectious Diseases and Cancer Research,*
[3]*School of Dentistry,* [9]*Department of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.;*
[4]*RIKEN BioResource Center, Tsukuba City, Japan;*
[5]*Saito Laboratory of Cell Technology, Yaita, Japan;*
[6]*Department of Biological Sciences, National Sun Yat-sen University, Kaohsiung, Taiwan, R.O.C.;*
[10]*Faculty of Molecular Preventive Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;*
[11]*Faculty of Science and Engineering, Tokushima Bunri University, Sanuki, Japan*

Abstract. *The cancer stem cell (CSC) hypothesis is an evolving concept of oncogenesis that has recently gained wide acceptance. By definition, CSCs exhibit continuous proliferation and self-renewal, and they have been proposed to play significant roles in oncogenesis, tumor growth, metastasis, chemoresistance, and cancer recurrence. The reprogramming of cancer cells using induced pluripotent stem cell (iPSC) technology is a potential strategy for the identification of CSC-related oncogenes and tumor-suppressor genes. This technology has some advantages for studying the interactions between CSC-related genes and the cancer microenvironment. This approach may also provide a useful platform for studying the mechanisms of CSCs underlying cancer initiation and progression. The present review summarizes the recent advances in cancer cell reprogramming using iPSC technology and discusses its potential clinical use and related drug screening.*

This article is freely accessible online.

Correspondence to: Kazunari K. Yokoyama, Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan, R.O.C. E-mail: kazu@kmu.edu.tw and Chang-Shen Lin, Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan, R.O.C. E-mail: csl@kmu.edu.tw

Key Words: Cancer cell reprogramming, cancer stem cell, drug screening, induced pluripotent stem cell, regenerative medicine, clinical application, review.

Cancer stem cells (CSCs) have been recognized as a small subset of cells within a tumor that are endowed with stem cell-like properties, including the abilities of self-renewal, pluripotency, cancer generation and drug resistance (1-7). The primary strategy used for inducing CSCs is to enrich the cells using classical stem cell markers such as CD13, CD24, CD44, CD47, CD90 and CD133, followed by other techniques including side-population analysis, sphere formation, and so on (8-11). This cell population is then transplanted into immunodeficient SCID mice to examine its *in vivo* tumorigenic potential (7-9). Such cells are examined further according to their cancer markers such as WNT, Notch, Hedgehog, transforming growth factor β, epithelial–mesenchymal transition (EMT)/mesenchymal–epithelial transition (MET) signaling proteins, and epigenetic factors (12-15). Putative CSC subpopulations that are capable of initiating tumor development at a lower cell number are tested for self-renewal capacity using serial dilutions of cells to identify the CSCs. In addition to these classical techniques, some techniques, such as reprogramming, are now a research focus, although the driver and the passenger mutation are present in the genome (12-15).

Current cancer cell-reprogramming techniques such as somatic cell nuclear transfer (16) and the generation of induced pluripotent stem cells (iPSCs) (17-19), are used to identify oncogenes, anti-oncogenes and epigenomes. The breakthrough came in 2006, when Takahashi and Yamanaka introduced the concept of iPSCs by generating stem cells

with properties related to those of embryonic stem cells (ESCs) (17, 18). The success in reprogramming a somatic cell into a stem cell-like state has led to the idea of reprogramming malignant cells back to their original state well before oncogenic transformation occurs. The generation of iPSCs from cancer cells may provide tools for exploring the mechanisms of tumor initiation and progression *in vitro*, for studying the plasticity of cancer cells and origin of CSCs, and for achieving cancer type-specific drug discovery (Figure 1).

However, these reprogramming methods remain a challenge because of two problems: the cancer-specific epigenetic state and the chromosomal aberrations or genetic mutations present in cancer cells. The epigenetic memory of the original cell type is critical for reprogramming and is related to the inefficient reprogramming that is caused by a failure to reset the epigenome to an ESC-like state (20). The epigenetic state attempts to reprogram cancer cells that may have produced incomplete resetting of the cancer-associated epigenome because of tumor heterogeneity and further accumulation of oncogenic mutations.

In 2014, the first-in-human clinical trial of iPSC-based cell therapy was conducted. A Japanese elderly woman with exudative age-related macular degeneration received implantation of a retinal pigment epithelial cell sheet that had been differentiated from iPSCs generated from fibroblasts from her own skin. Although this sheet did not improve the patient's vision, it did halt disease progression (21, 22). In 2015, in a second clinical trial using such sheet, the genetic mutations invoIved were identified. However, there was no clear confirmation that these mutations could lead directly to advanced effects of diseases (23, 24). In order to advance iPSC-based novel therapies, it is critical to determine how and when these mutations occur and whether they actually lead to harmful effects. In the above trials, the patients were elderly individuals; thus, the occurrence of mutations might have been facilitated. In order to avoid these difficulties, Yamanaka's group used human leucocyte antigen (HLA)-matched young patients in subsequent trials of iPSC-based cell therapy, which is expect to be more successful (22).

Therefore, cancer cell reprogramming is currently limited to certain cancer types and cancer-specific markers in the epigenome; this impedes successful reprogramming. Moreover, the underlying mechanisms have not been fully elucidated. Thus, further elucidation of these issues may help prevent these alterations. Nevertheless, we expect that this iPSC-based technology and therapy will be a breakthrough in the prevention of cancer generation and progression. In this review, we summarize the features of the iPSC-like cells derived from human cancer for cell therapy and discuss both their merits and demerits regarding clinical and pharmaceutical applications.

The Bilateral Character of Cancer-specific iPSC-Iike Cells

The difficulties encountered in the reprogramming of cancer cells include cancer-specific genetic mutations, chromosomal rearrangements, accumulation of DNA damage, and reprogramming-triggered cellular senescence (25-27). Despite these obstacles, many studies have reported the generation of iPSCs from cancer cells, as summarized in Table I. This has covered a range of cancer cells, including melanoma (28, 29), prostatic (28), gastrointestinal (30), chronic myeloid leukemia (CML) (31), lung (32), breast (33), glioblastoma (34), and sarcoma (35).

The initial success in this field consisted in the successful reprogramming of colon metastatic cells and PC-3 prostate metastatic cells *via* the expression of intronic *miR-302* (28). Subsequently, Miyoshi *et al*. performed a series of reprogramming studies with different methods using 20 gastrointestinal cancer cell lines, and obtained successful results for eight of them (30). Transduction by a combination of retroviral- or lentiviral-based Octamer-binding protein 4 (*OCT4*), SRY (sex determining region Y)-box 2 (*SOX2*), Krüppel-like factor (*KLF4*), Cellular myelocytomatosis viral oncogene homolog (*c-MYC*) (*OSKM*), B cell lymphoma-2 (*BCL2*), Kirsten rat sarcoma viral oncogene homolog (*kRAS*), Lin 28 homolog (*LIN28*), Nanog homeobox (*NANOG*), then transforming growth factor was added, and shRNA for tumor-suppressor genes for each cell line was used initially to obtain iPSC-like cells that re-expressed *NANOG*. The eight cell lines from which iPSCs were generated were derived from cholangiocellular carcinoma (HuCCT-1), colorectal (DLD1, HT29), hepatocellular (PLC), gastric (TMKN45), esophageal (YE10), and pancreatic (MIAPPaCa-2, PAV-1). The resultant iPSC-like cells were less tumorigenic as compared with their parental cell lines. Similarly, Noguchi *et al*. found that PANC1 cells were easily reprogrammed, while three other cell lines, MIAPaCa-2, PSN-1, and AsPC-1, were not (36). Iskender *et al*. also reported the generation of iPSCs derived from bladder carcinoma T24 cells, but another bladder carcinoma cell line, HTB-9, could not be induced to reprogram (37). Thus, the success of the generation of iPSCs from cancer cells seems to be cell-type specific. This is one of the problems with this technology.

Another problem encountered in this field of research is the lower efficiency of cancer cell reprogramming. This low efficiency in iPSC generation from cancer cells suggests the presence of multiple mechanisms that might be involved in the regulation of reprogramming (37, 38). Mathieu *et al*. reported that reprogramming factors and Hypoxia-inducible factor 1 alpha (HIF1α) accelerated the induction of iPSCs from the A549 lung carcinoma cell line, suggesting that reprogramming is enhanced by a cumulative effect of environmental hypoxia (32). Moreover, Mohyeldin *et al*.

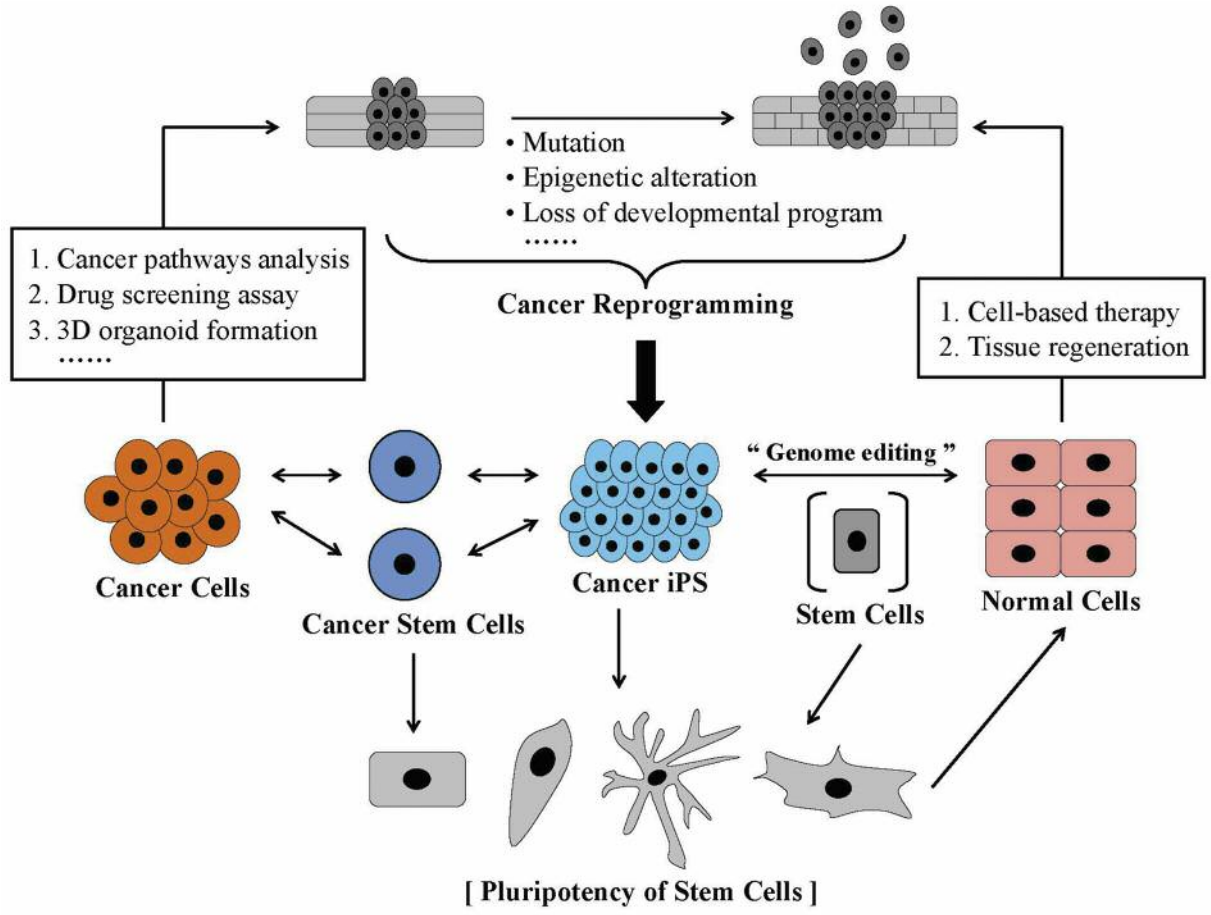

Figure 1. *Schematic representation of use of cancer-derived induced Pluripotent stem cell (iPSC)s for cancer biology. Tissue resources may be used to develop human cancer specific iPSCs lines and generate cancer stem cell (CSC)s mechanistic studies of cancer remodeling and drug screening or develop cell-based therapy of human cancer using genomic editing and induced differentiation from organoid 3D cells.*

showed that low oxygen levels promote the self-renewing capacity of stem cells (39). Hypoxia activated the expression of stemness genes, such as *OKM* and *NANOG*, and stem-cell-associated miRNAs, in different cancer cell lines that shared an overlapping gene expression signature with human ESC lines (32).

Hematopoietic malignancy with chromosome rearrangement is another challenging issue; disease-specific iPSCs possessing the genetic abnormalities of hematological malignancies would provide an efficient platform for studying pathogenesis. Carette *et al*. generated iPSCs derived from the CML cell line KBM7 carrying the fusion gene of the breakpoint cluster region protein (BCR)-breakpoint cluster region protein (BCR) (*BCR–ABL*) *via* defined factors OSKM (31). An acute myeloid leukemia (AML) mouse model was also generated by retroviral overexpression encoded the human mixed-lineage leukemia-*AF9* (*MLL–AF9*) fusion gene in hematopoietic cells from transgenic mice that carried deoxycycline-inducible four OSKM genes. Upon deoxycycline addition, the MLL–AF9-expressing leukemia cells were efficiently converted into iPSCs that were capable of forming teratomas and producing chimeras. Most of the chimeric mice developed AML spontaneously (40).

Moreover, reports of the generation of iPSCs generated from human primary malignant cells are scarce and are limited to cancers such as leukemia (41-44) and pancreatic cancer (45). Hu *et al*. (41) used the transgene-free iPSC technology to express *OSKM, NANOG, LIN28*, and Simian vacuolating virus 40 large T antigen (*SV40 LT*) genes in primary human lymphoblasts from a BCR–ABL-positive patient with CML (41). Kumano *et al*. produced iPSCs from samples from imatinib-sensitive patients with CML that became resistant to imatinib despite the expression of the *BCR–ABL* oncogene (42). Gandre-Babbe *et al*. (43) and

Table I. *Summary of studies of reprogramming of human cancer cells to induce pluripotent stem cells (iPSC). Recent reports also demonstrated the success in reducing the tumorigenicity of cancer cells (51, 80-82), or not changing the plasticity of cancer cells (80, 81, 83-85), even exhibiting strong cancerous features such as cancer stem cells (81), even these heterogeneous outputs are due to the status of p53 (86). Modified from the Table in Izgi et al. (87).*

Human cancer types	Cell line	Karyotype	Method	Epigenesis	Teratoma/ tumor formation	Comments	Reference
Colonic Prostatic	Colon PC-3		Retrovirus miR-302 family	Demethylation		Similar expression of pluripotent marker to ESCs	28
Mouse melanoma	R545 (Ras induced)	Trisomy Chromosome 8 & Chromosome 11	Lentivirus OSK	Demethylation of OCT4 & NANOG promoters	Yes	No tumor formation in the absence of DOX	29
CML (blast crisis stage)	KBM7	Tetraploid chromosome 9 & chromosome 22 Ph(+)	Retrovirus OSKM	Partial demethylation of OCT4 & NANOG promotors	Yes	Differentiate into neural or hematopoietic like cells Non-hematopoietic derivatives are imatinib-resistant	31
			Retrovirus OSK (Incomplete)	Unknown			
Colorectal Esophageal Gastric Hepatocellular cancer Pancreatic cancer Cholangio-cellular cancer	DLD-1, HT-29 TE-10 MKN45 PLC MIApaCa-2, PANC-1 HuCC-T1	Abnormal	Combination of retrovirus or lentivirus OKSM, NANOG, LIN28, BCL2, kRAS and shRNA to tumor suppressor	Demethylation of *NANOG* promoter Histone modification		Slower proliferation Sensitivity to differentiation inducing agents & chemotherapeutic agents Reduced tumorigenicity High expression of $p16^{Ink4a}$ and p53 in embryoid body	30
Gastrointestinal cancer cells		Abnormal	Retrovirus & Lentivirus of OSKM + lipofectamine		High tumorigenicity	Long term culture → down-regulation of endogenous OSK and up-regulation of C-MYC	83
CML (chronic phase)	Patient-derived bone marrow cells	Abnormal	Episomal vector of OSKM, Nanog, LIN 28, SV40LT			BCR-ABL fusion in iPSCs	41
Lung adenocarcinoma	A549	Abnormal	Retrovirus HIF1α & HIF2α and then lentivirus OSKM	Partially demethylated OCT4	High tumorigenicity → more aggressive and invasive iPSCs	Partial reprogramming	32
CML	Bone marrow cells of a patient with CML		Retrovirus OSKM			Imatinib resistance Differentiated into hematopoietic lineage & reversed sensitivity to Imatinib	42
Colorectal	HCT116	Abnormal	Lentivirus OSLN + hypoxia		Reduced tumorigenesis		86
Non-small cell lung	H358, H460, IMR90	Abnormal	Lentivirus OSKM	Reversed methylation partial and transcription of dysregulated genes	Reduced tumorigenicity		52
PDAC		Aberrant karyotype (~20 chromosome aberration)	Lentivirus OSKM	Demethylation *OCT4* & *NANOG* promoters	Mostly endodermal Pancreatic in the epithelial neoplasia	Tumor recapitulated early and advanced stage of PDAC	45
Medulloblastoma	DAOY	Abnormal	Lentivirus JDP2 + OCT4 or OSKM	Demethylation	Teratoma Increased tumorigenicity	Enhanced tumor formation JDP2 + OCT4 induced to generate iPSCs	85

Table I. *Continued*

Table I. *Continued*

Human cancer types	Cell line	Karyotype	Method	Epigenesis	Teratoma/ tumor formation	Comments	Reference
Junenile myelomonocytic leukemia	Patient-derived mononuclear cells with E76K missense in PTPN11 gene	Abnormal	Lentivirus OSKM			Increase of GM-CSF Increased proliferation and differentiation	43
Breast	MCF-7	Abnormal	Retrovirus OSKM			Enhance SOX2 and cancer stem cell characters	33
Osteosarcoma Ewing's sarcoma Liposarcoma	SAOS2, HOS, MG63 SHNEP SW872	Abnormal	Lentivirus OSKM, N, L		Reduced tumorigenicity	More pluripotency features Differentiate into mature connective tissue and red blood cells	34
GBM	GBM neural stem (GNS) cell line	Abnormal	PiggyBac transposon vector system – OCT4, KLF4		Remained tumorigenic	Differentiation to neural progenitor	34
Colorectal	SW480, DLD-1	Abnormal	Retrovirus OSK		Enhanced tumorigenicity Failed to be teratogenic	Cancer stem cell phenotype	49
MDS	Patient with del (7q) - MDS	Abnormal	Lentivirus OSKM			Recapitulated feature of disease-associated phenotypes Impaired hematopoietic differentiation	44
LFS	Patient with G245D missense in p53	Mutation	Sendaivirus OSKM		Defective tumorigenicity	Recapitulated feature of osteosarcoma-associated LFS Defective osteoblastic differentiation	80
Ewing sarcoma	CHLA-10	Abnormal	Episomal OSKM		Tumorigenic	Ewing histopathology Recovery of drug sensitivity	51
Pancreatic	PANC1	Abnormal	Sendaivirus OSKM			C-MET-high cells with more susceptible to reprogramming than C-MET-low cells	36
Bladder	T24 HTB9	Abnormal	Sendaivirus OSKM			T24 was susceptible to reprogramming HTB-9 cells failed to generate iPSCs	37
EWS-FLI1-induced osteosarcoma	Mouse EXS-FLI1 dependent osteosarcoma	Abnormal	Episomal OSNK		Tumorigenic	EWS-FLI1 sarcoma contributes to secondary development after osteogenic differentiation	84
Melanoma	Tumor-infiltration lymphocyte	Normal karyotype	Sendaivirus OSKM			Generate patient- and tumor-specific polyclonal T-cells	38
Ataxia–Telangiectasia (A-T)	PBL	Abnormal (A-T)	Episomal OSKM		Teratoma	*In vitro* modeling of A-T	82
Hepatocarcinoma	HepG2	Abnormal	Lentivirus OSKM + shp53		Teratoma Tumorigenic	Generated liver cancer stem-like cells (O + JDP2)	81
Melanoma	HT-144 (BRAF V600E), SKMEL147, Mewo	Abnormal	Episomal OSK	Demethylation	Teratoma Reduced tumorigenicity (differential tumorigenicity)	Resistant to MAPK inhibition	82

PDAC, Pancreatic ductal adenocarcinoma; MDS, myelodysplastic syndromes; LFS, Li–Fraumeni syndrome; GBM, glioblastoma multiforme; CML, chronic myeloid leukemia; C-MET, Tyrosine-protein kinase MET; DOX, doxycycline; ESCs, embryonic stem cells; GM-CSF, granulocyte macrophage colony-stimulating factor; HIF1a, hypoxia-inducible factor 1-alpha; HIF 2a, hypoxia-inducible factor 2-alpha; K, KLF4; M, c-MYC; MAPK, mitogen-activated protein kinases; N, NANOG; O, Octamer-binding protein 4 (OCT4); S, SRY(sex determining region Y)-box 2 (SOX2); shp53, short hairpin p53.

Kotini *et al*. (44) reported that the reprogramming of cancer cells was feasible despite the presence of genomic alterations in the parental cells, and that iPSCs derived from patients with juvenile myelomonocyte leukemia and with myelodysplatic syndrome recapitulated the disease-associated phenotype. Similarly, pancreatic-cancer-derived iPSC-like cells were also successfully generated from a parental pancreatic ductal adenocarcinoma with a *kRAS*G12D mutation (45). Therefore, a similar concept is found in the reprogramming of normal somatic cells, in which reprogramming-induced multiple genetic/epigenetic abnormalities did not interfere with the differentiation capacity of the resulting iPSCs (46-48). Although expression of reprogramming genes was found to be successful in various primary patient samples of hematological malignancies, Liu *et al*. reported that NOTCH1-induced T-acute lymphoblastic leukemia could not be reprogrammed into a pluripotent state (40). Therefore, the reprogramming of cancer cells needs to be optimized for each cancer type. For example, Utikal *et al*. showed that the R545 melanoma cell line could be reprogrammed into iPSCs by introducing OCT4-KLF4-c-MYC (*OKM*), without ectopic SOX2 requirement (29). The resultant iPSCs were used to generate higher-degree chimeric mice that exhibited competent germline transmission. In contrast, Oshima *et al*. showed the induction of CSC features in colon cancer cells upon the introduction of OCT4-SOX2-KLF4 (*OSK*), and found that a subset of colon cancer cells gained cancer properties expressed defined colon CSC markers but not to teratomas *in vivo* (49). This different reprogramming might be caused by heterogeneity in plasticity or epigenesis.

Interestingly, Jaenisch's group examined reprogramming activity using nuclear transplantation techniques (transplantation of nuclei from melanoma, leukemia, lymphoma, and breast cancer cells into enucleated oocytes) (50). In fact, all nuclei from primary leukemia and lymphoma cells cannot be reprogramed. A modest percentage of the transplanted nuclei from all cancer cells and transplanted tumors were reprogrammed, and the surviving oocytes went on to develop into blastocysts. By contrast, only blastocysts derived from the melanoma yielded ESCs, indicating that not all cancer genomes can be epigenetically reprogrammed to full pluripotency using the nuclear transplantation. Moreover, chimeras were generated only by using the melanoma nuclear-transferred ESCs. However, the chimeras developed earlier and exhibited higher expansion into tumor cells compared with the original nucleus-donor mouse model. These studies indicate that reprogramming of a primary tumor cells is more difficult in mouse models, and that further technological progress is needed to be able to generate reliable iPSC models of cancer.

Epigenetic Remodeling of Cancer Cells

Epigenetic changes in cancer cells result in reduced or increased aggressive phenotypes of partially reprogrammed iPSCs or iPSC-like cells. Regarding DNA methylation, Moore *et al*. reported that iPSCs from cancer cells exhibited distinct hypomethylation of the densely methylated regions of the genome, which are specific for cancer cells (51). Stricker *et al*. showed that glioblastoma cell lines derived from patients with high aneuploidy exhibited erasure of cancer-specific DNA methylation and could be reprogrammed (34). Moreover, reprogramming antagonized the DNA methylations that are significant for non-small cell lung cancer (NSCLC) cell lines, and differentiation of NSCLC-derived iPSCs *in vitro* did not restore the tumor-specific epigenetic modification (52). iPSCs from glioblastoma-derived neural stem cells exhibited reduced ability to infiltrate into surrounding tissues, suggesting suppression of their aggressive character upon reprogramming (34). Zhang *et al*. reprogrammed cells from three osteosarcoma, two liposarcoma, and a sarcoma of unknown origin, which altered the epigenetic feature of oncogenes (35). Tumor-suppressor genes render cells with a less aggressive tumor phenotype. However, some studies have suggested the acquisition of sensitivity to anticancer agents in the reprogramming of iPSCs, which is not necessarily an indicator of repression of the malignancy, but shows increased drug sensitivity compared with the parental cells (30). The reactivation of some tumor-suppressor genes, such as $p16^{Ink4a}$, in iPSCs might lead to increasing chemosensitivity as well as the repressing proliferation and invasiveness in reprogrammed cancer cells (30). Although not all cancer reprogramming studies have analyzed the tumorigenic potential or drug responsiveness of the resulting iPSCs (31, 42, 53), the results of studies contradict the outcomes of Miyoshi *et al*. (30).

The tumor-suppressor gene products are known to play a critical role in reprogramming to generate iPSCs (54); however, more evidence is needed to draw a conclusion in terms of the role of the suppressor proteins in cancer-specific reprogramming. BMI1 in polycomb repressive complex 1 was demonstrated to increase reprogramming efficiency by replacing the function of KLF4 and c-MYC (55, 56). Another member of the polycomb repressive complex 2, EZH2, is also critical for reprogramming; forced expression of EZH2 enhances, while knockdown of EZH2 impairs, the generation of iPSCs (57-59). The epigenetic study of cancer cells exhibited aberrant epigenetic regulation of the p53-Inhibitors of cyclin-dependent kinase (INK) family network. Thus, the absence or reduced expression of p53 and $p21^{CIP1}$ favored the generation of iPSCs (60-62). Epigenetic silencing of tumor-suppressor genes, such as though aberrant methylation of the $p16^{INK4A}$ promoter, has been shown to be reversed by reprogramming (63). Therefore,

the reprogramming of cancer cells and overcoming of the barriers to pluripotency remain to be solved.

Common epigenetic processes might be involved in reprogramming and in the development of certain cancer types. In fact, global changes in epigenetic modifications that occur in normal cells and cancer cells were demonstrated to be bidirectional rather than unidirectional. Therefore, the application of reprogramming techniques to cancer cells might promote our understanding of the cancer-specific epigenome and elucidate the overlapping mechanisms shared by cancer-initiating and pluripotent cells.

Is it possible to reprogram cells *via* modification of the epigenetic state? A few authors have reported such reprogramming in the mouse. Hou *et al*. showed that a combination of small molecules is sufficient for pluripotency and is dispensable for reprogramming in mouse somatic cells (64). Growing evidence suggests that a combination of small molecules in mouse cells could compensate for exogenous reprogramming factors and generated iPSC-like cells with expression profiles and epigenesis similar to those of ESCs (65). Thus, for certain cell types, epigenomic editing could replace the ectopic expression of transcription factors for reprogramming, while for most cell types, the overcoming of epigenetic obstacles warrants a combination of mechanisms induced by forced expression of reprogramming factors and other modifications.

Reprogramming efficiency has been shown to be improved upon treatment with small molecules including inhibitors of DNA methyltransferase, histone deacetylase, WNT signal modulators, modulators of cell senescence, and metabolism (66). Cell origin thoroughly affects reprogramming efficiency, as iPSC induction does not reset the epigenetic memory completely, and the memory of the donor cell may be retained in the iPSCs (67). Incomplete reprogramming with inherited epigenetic memory generates iPSCs that have a tendency to differentiate toward the original lineage (68). Although reprogramming efficiency was further increased after combinational treatment with small molecules, transcription factors, and signaling pathway regulators, efforts should be focused on elucidating the mechanisms that direct terminally differentiated cells to erase their somatic epigenetics and gain pluripotency (69-71). Moreover, some of these observations were made in the mouse, not in humans. Thus, human iPSCs from human cancer cells need to be examined further, and additional information regarding the molecular relationship between epigenetic control and reprogramming should be collected.

Potential Application in Biomedical Research

Human cancer-derived iPSCs can be used to preserve unique genotypes by banking cells that can be differentiated into many cell types. The cancer-derived iPSC model is used for studying the mutation of cancer-related genes and epigenetic alterations in the genome in order to understand the molecular mechanisms underlying tumorigenesis in humans. The use of iPSC technologies has both advantages and disadvantages compared with traditional approaches using cancer cell lines and animal models. High-throughput drug screening using patient-specific iPSCs has been receiving growing attention. Chemotherapy takes a huge toll on patients with cancer because of its undesirable side-effects. A differentiated cytotoxicity screen could lead to the development of drugs that are more specific to their target cells.

Efforts to harness the merits of iPSC technology have been carried out for various neurological disorders (72) and diabetic cardiomyopathy (73). Current recombinant technologies enable precise genomic manipulation in diseased cells. For example, the efficiency of iPSC production can be improved through use of techniques including episomal plasmids, lentivirus-, adenovirus-, or sendai virus-mediated gene transfers. Moreover, the feasibility of genetic manipulation in iPSCs has been demonstrated using several technologies such as knockdown, knockout, and gene correction using homologous recombination, combined with genome-editing tools such as zinc-finger nucleases, Transcription activator-like effector nuclease (TALEN)s, and the Clustered regularly interspaced short palindromic repeats (CRISPER)- CRISPR associated protein 9 (CAS9) system (74, 75). Genetically defective cells could be corrected *in vitro* and reintroduced into patients. The autologous transplantation approach has been shown to be effective in principle using a humanized mouse model of sickle cell anemia (76). Human iPSCs are a potential source of cells for tissue reconstruction in the long term (77). Saki *et al*. reported that transplanted hematopoietic precursor cells can be generated from iPSCs, potentially offering new cell sources for cell reconstitution in patients with hematological cancer after treatment (78). Recently, AML patient-derived dermal fibroblasts were reprogrammed into normal iPSCs that did not carry any chromosomal aberrations of the patient's bone marrow cells, and they differentiated into normal hematopoietic progenitor cells (78). The HLA-matched iPSC sources at the iPSC bank of Kyoto University or the RIKEN Cell Bank are now prepared for clinical use (http://www.cira.kyoto-u.ac.jp/e/research/stock.html and http://cell.brc.riken.jp/en/, respectively). The use of three-dimensional (3D) organoid technologies to engineer tissues, such as stomach, small intestine, colon, pancreas and liver, are expected to bring about great advances regarding how we can model human disorders, perform drug screenings, and engineer replacement tissues or organs (79). Human organoid cultures are useful for studies in regenerative medicine and for the therapeutic screening of drugs and small molecules. These engineered 3D tissues can replace intact tissues in the cancer research because they are histologically and functionally more faithful to their *in vivo* counterparts.

Conclusion

The generation of patient-specific iPSCs from various tissues is revolutionizing the way in which we approach human disease modeling, novel drug development, and autologous/allogenic cell therapy of disorders. In particular, cancer iPSCs offer a new paradigm in cancer modeling and tissue regeneration. Cancer-derived iPSCs may enhance our understanding of the features of tumorigenesis, the effects of microenvironments, and how epigenetic events contribute to the development of various cancer types. This information could be expected to enable the establishment of drug screening platforms, the development of more targetable and less toxic therapies, and effective tissue reconstitution. The study of the reprograming of cancer cells and efforts to harness the versatility of iPSCs for cancer remodeling and for screening effective drugs should contribute to further progress in our understanding of cancer biology.

Competing Interests

The Authors declare that they have no competing interests.

Acknowledgements

This work was supported in part by MOST 104-2320-B-037-033-My2, and MOST 104-2314-B-037-002, MOST 104-2314-B-037-043 from the Ministry of Science and Technology; NHRI-EX106-10416S1, from the National Health Research Institutes in Taiwan; and KMU-TP105G01, KMU-TP105E21, and KMU-DT106006 from Kaohsiung Medical University in Taiwan. The Authors also thank Wen-Hsin Lin for drawing the Figure and preparing the Table.

References

1 Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, Minden M, Paterson B, Caligiuri MA and Dick JE: A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature *367*: 645-648, 1994.

2 Shibue T and Weinberg RA: EMT, CSCs and drug resistance: the mechanistic link and clinical implications. Nat Rev Clin Oncol, 2017. doi:10.1038/nrclinonc.2017.44. [Epub ahead of print]

3 Laplane L, Beke A, Vainchenker W and Solary E: Concise Review: Induced Pluripotent Stem Cells as New Model Systems in Oncology. Stem Cells *33*: 2887-2892, 2015.

4 Friedmann-Morvinski D and Verma IM: Dedifferentiation and reprogramming: origins of cancer stem cells. EMBO Rep *15*: 244-253, 2014.

5 Medema JP: Cancer stem cells: the challenges ahead. Nature Cell Biol *15*: 338-344, 2013.

6 Visvader JE and Lindeman GJ: Cancer stem cells: current status and evolving complexities. Cell Stem Cell *10*: 717-728, 2012.

7 Magee JA, Piskounova E and Morrison SJ: Cancer stem cells: impact, heterogeneity and uncertainty. Cancer Cell *21*: 283-296, 2012.

8 Ishiguro T, Ohata H, Sato A, Yamawaki K, Enomoto T and Okamoto K: Tumor-derived spheroids: Relevance to cancer stem cells and clinical applications. Cancer Science *108*: 283-289, 2017.

9 Chiba T, Kita K, Zheng YW, Yokosuka O, Saisho H, Iwama A, Nakauchi H and Taniguchi H: Side population purified from hepatocellular carcinoma cells harbors cancer stem cell-like properties. Hepatology *44*: 240-251, 2006.

10 Ma S, Chan KW, Lee TK, Tang KH, Wo JY, Zheng BJ and Guan XY: Aldehyde dehydrogenase discriminates the CD133 liver cancer stem cell populations. Mol Cancer Res *6*: 1146-1153, 2008.

11 Cardinale V, Renzi A, Carpino G, Torrice A, Bragazzi MC, Giuliante F, DeRose AM, Fraveto A, Onori P, Napoletano C, Franchitto A, Cantafora A, Grazi G, Caporaso N, D'Argenio G, Alpini G, Reid LM, Gaudio E and Alvaro D: Profiles of cancer stem cell subpopulations in cholangiocarcinomas. The Am J Pathol *185*: 1724-1739, 2015.

12 Chen J, McKay RM and Parada LF: Malignant glioma: lessons from genomics, mouse models and stem cells. Cell *149*: 36-47, 2012.

13 Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr. and Kinzler KW: Cancer genome landscapes. Science *339*: 1546-1558, 2013.

14 Pon JR and Marra MA: Driver and passenger mutations in cancer. Ann Rev Pathol *10*: 25-50, 2015.

15 De S and Ganesan S: Looking beyond drivers and passengers in cancer genome sequencing data. Ann Oncol *28*: 938-945, 2017.

16 Gurdon JB and Wilmut I: Nuclear transfer to eggs and oocytes. Cold Spring Harb Perspect Biol *3*: a002659, 2011.

17 Takahashi K and Yamanaka S: Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell *126*: 663-676, 2006.

18 Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K and Yamanaka S: Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell *131*: 861-872, 2007.

19 Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, Slukvin, II and Thomson JA: Induced pluripotent stem cell lines derived from human somatic cells. Science *318*: 1917-1920, 2007.

20 Papp B and Plath K: Reprogramming to pluripotency: stepwise resetting of the epigenetic landscape. Cell Res *21*: 486-501, 2011.

21 Kamao H, Mandai M, Okamoto S, Sakai N, Suga A, Sugita S, Kiryu J and Takahashi M: Characterization of human induced pluripotent stem cell-derived retinal pigment epithelium cell sheets aiming for clinical application. Stem Cell Reports *2*: 205-218, 2014.

22 Mandai M, Watanabe A, Kurimoto Y, Hirami Y, Morinaga C, Daimon T, Fujihara M, Akimaru H, Sakai N, Shibata Y, Terada M, Nomiya Y, Tanishima S, Nakamura M, Kamao H, Sugita S, Onishi A, Ito T, Fujita K, Kawamata S, Go MJ, Shinohara C, Hata KI, Sawada M, Yamamoto M, Ohta S, Ohara Y, Yoshida K, Kuwahara J, Kitano Y, Amano N, Umekage M, Kitaoka F, Tanaka A, Okada C, Takasu N, Ogawa S, Yamanaka S and Takahashi M: Autologous induced stem-cell-derived retinal cells for macular degeneration. New Engl J Med *376*: 1038-1046, 2017.

23 Chakradhar S: An eye to the future: Researchers debate best path for stem cell-derived therapies. Nature Med *22*: 116-119, 2016.

24 Garber K: RIKEN suspends first clinical trial involving induced pluripotent stem cells. Nat Biotechnol *33*: 890-891, 2015.

25 Banito A and Gil J: Induced pluripotent stem cells and senescence: learning the biology to improve the technology. EMBO Rep *11*: 353-359, 2010.
26 Banito A, Rashid ST, Acosta JC, Li S, Pereira CF, Geti I, Pinho S, Silva JC, Azuara V, Walsh M, Vallier L and Gil J: Senescence impairs successful reprogramming to pluripotent stem cells. Genes Dev *23*: 2134-2139, 2009.
27 Ramos-Mejia V, Fraga MF and Menendez P: iPSCs from cancer cells: challenges and opportunities. Trends Mol Med *18*: 245-247, 2012.
28 Lin SL, Chang DC, Chang-Lin S, Lin CH, Wu DT, Chen DT and Ying SY: Mir-302 reprograms human skin cancer cells into a pluripotent ES-cell-like state. RNA *14*: 2115-2124, 2008.
29 Utikal J, Maherali N, Kulalert W and Hochedlinger K: Sox2 is dispensable for the reprogramming of melanocytes and melanoma cells into induced pluripotent stem cells. J Cell Sci *122*: 3502-3510, 2009.
30 Miyoshi N, Ishii H, Nagai K, Hoshino H, Mimori K, Tanaka F, Nagano H, Sekimoto M, Doki Y and Mori M: Defined factors induce reprogramming of gastrointestinal cancer cells. Proc Natl Acad Sci USA *107*: 40-45, 2010.
31 Carette JE, Pruszak J, Varadarajan M, Blomen VA, Gokhale S, Camargo FD, Wernig M, Jaenisch R and Brummelkamp TR: Generation of iPSCs from cultured human malignant cells. Blood *115*: 4039-4042, 2010.
32 Mathieu J, Zhang Z, Zhou W, Wang AJ, Heddleston JM, Pinna CM, Hubaud A, Stadler B, Choi M, Bar M, Tewari M, Liu A, Vessella R, Rostomily R, Born D, Horwitz M, Ware C, Blau CA, Cleary MA, Rich JN and Ruohola-Baker H: Long-term culture following ES-like gene-induced markers in cancer cells. Cancer Res *71*: 4640-4652, 2011.
33 Corominas-Faja B, Cufi S, Oliveras-Ferraros C, Cuyas E, Lopez-Bonet E, Lupu R, Alarcon T, Vellon L, Iglesias JM, Leis O, Martin AG, Vazquez-Martin A and Menendez JA: Nuclear reprogramming of luminal-like breast cancer cells generates Sox2-overexpressing cancer stem-like cellular states harboring transcriptional activation of the mTOR pathway. Cell Cycle *12*: 3109-3124, 2013.
34 Stricker SH, Feber A, Engstrom PG, Caren H, Kurian KM, Takashima Y, Watts C, Way M, Dirks P, Bertone P, Smith A, Beck S and Pollard SM: Widespread resetting of DNA methylation in glioblastoma-initiating cells suppresses malignant cellular behavior in a lineage-dependent manner. Genes Dev *27*: 654-669, 2013.
35 Zhang X, Cruz FD, Terry M, Remotti F and Matushansky I: Terminal differentiation and loss of tumorigenicity of human cancers *via* pluripotency-based reprogramming. Oncogene *32*: 2249-2260, 2013.
36 Noguchi K, Eguchi H, Konno M, Kawamoto K, Nishida N, Koseki J, Wada H, Marubashi S, Nagano H, Doki Y, Mori M and Ishii H: Susceptibility of pancreatic cancer stem cells to reprogramming. Cancer Sci *106*: 1182-1187, 2015.
37 Iskender B, Izgi K and Canatan H: Reprogramming bladder cancer cells for studying cancer initiation and progression. Tumour Biol *37*: 13237-13245, 2016.
38 Saito S, Lin YC, Tsai MH, Lin CS, Murayama Y, Sato R and Yokoyama KK: Emerging roles of hypoxia-inducible factors and reactive oxygen species in cancer and pluripotent stem cells. Kaohsiung J Med Sci *31*: 279-286, 2015.
39 Mohyeldin A, Garzon-Muvdi T and Quinones-Hinojosa A: Oxygen in stem cell biology: a critical component of the stem cell niche. Cell Stem Cell *7*: 150-161, 2010.
40 Liu Y, Cheng H, Gao S, Lu X, He F, Hu L, Hou D, Zou Z, Li Y, Zhang H, Xu J, Kang L, Wang Q, Yuan W, Gao S and Cheng T: Reprogramming of MLL-AF9 leukemia cells into pluripotent stem cells. Leukemia *28*: 1071-1080, 2014.
41 Hu K, Yu J, Suknuntha K, Tian S, Montgomery K, Choi KD, Stewart R, Thomson JA and Slukvin, II: Efficient generation of transgene-free induced pluripotent stem cells from normal and neoplastic bone marrow and cord blood mononuclear cells. Blood *117*: e109-119, 2011.
42 Kumano K, Arai S, Hosoi M, Taoka K, Takayama N, Otsu M, Nagae G, Ueda K, Nakazaki K, Kamikubo Y, Eto K, Aburatani H, Nakauchi H and Kurokawa M: Generation of induced pluripotent stem cells from primary chronic myelogenous leukemia patient samples. Blood *119*: 6234-6242, 2012.
43 Gandre-Babbe S, Paluru P, Aribeana C, Chou ST, Bresolin S, Lu L, Sullivan SK, Tasian SK, Weng J, Favre H, Choi JK, French DL, Loh ML and Weiss MJ: Patient-derived induced pluripotent stem cells recapitulate hematopoietic abnormalities of juvenile myelomonocytic leukemia. Blood *121*: 4925-4929, 2013.
44 Kotini AG, Chang CJ, Boussaad I, Delrow JJ, Dolezal EK, Nagulapally AB, Perna F, Fishbein GA, Klimek VM, Hawkins RD, Huangfu D, Murry CE, Graubert T, Nimer SD and Papapetrou EP: Functional analysis of a chromosomal deletion associated with myelodysplastic syndromes using isogenic human induced pluripotent stem cells. Nat Biotechnol *33*: 646-655, 2015.
45 Kim J, Hoffman JP, Alpaugh RK, Rhim AD, Reichert M, Stanger BZ, Furth EE, Sepulveda AR, Yuan CX, Won KJ, Donahue G, Sands J, Gumbs AA and Zaret KS: An iPSC line from human pancreatic ductal adenocarcinoma undergoes early to invasive stages of pancreatic cancer progression. Cell Rep *3*: 2088-2099, 2013.
46 Hussein SM, Batada NN, Vuoristo S, Ching RW, Autio R, Narva E, Ng S, Sourour M, Hamalainen R, Olsson C, Lundin K, Mikkola M, Trokovic R, Peitz M, Brustle O, Bazett-Jones DP, Alitalo K, Lahesmaa R, Nagy A and Otonkoski T: Copy number variation and selection during reprogramming to pluripotency. Nature *471*: 58-62, 2011.
47 Lister R, Pelizzola M, Kida YS, Hawkins RD, Nery JR, Hon G, Antosiewicz-Bourget J, O'Malley R, Castanon R, Klugman S, Downes M, Yu R, Stewart R, Ren B, Thomson JA, Evans RM and Ecker JR: Hotspots of aberrant epigenomic reprogramming in human induced pluripotent stem cells. Nature *471*: 68-73, 2011.
48 Mayshar Y, Ben-David U, Lavon N, Biancotti JC, Yakir B, Clark AT, Plath K, Lowry WE and Benvenisty N: Identification and classification of chromosomal aberrations in human induced pluripotent stem cells. Cell Stem Cell *7*: 521-531, 2010.
49 Oshima N, Yamada Y, Nagayama S, Kawada K, Hasegawa S, Okabe H, Sakai Y and Aoi T: Induction of cancer stem cell properties in colon cancer cells by defined factors. PLoS One *9*: e101735, 2014.
50 Hochedlinger K, Blelloch R, Brennan C, Yamada Y, Kim M, Chin L and Jaenisch R: Reprogramming of a melanoma genome by nuclear transplantation. Genes Dev *18*: 1875-1885, 2004.
51 Moore JBt, Loeb DM, Hong KU, Sorensen PH, Triche TJ, Lee DW, Barbato MI and Arceci RJ: Epigenetic reprogramming and re-differentiation of a Ewing sarcoma cell line. Front Cell Dev Biol *3*: 15, 2015.

52 Mahalingam D, Kong CM, Lai J, Tay LL, Yang H and Wang X: Reversal of aberrant cancer methylome and transcriptome upon direct reprogramming of lung cancer cells. Sci Rep *2*: 592, 2012.
53 Islam SM, Suenaga Y, Takatori A, Ueda Y, Kaneko Y, Kawana H, Itami M, Ohira M, Yokoi S and Nakagawara A: Sendai virus-mediated expression of reprogramming factors promotes plasticity of human neuroblastoma cells. Cancer Sci *106*: 1351-1361, 2015.
54 Lin YC, Murayama Y, Hashimoto K, Nakamura Y, Lin CS, Yokoyama KK and Saito S: Role of tumor suppressor genes in the cancer-associated reprogramming of human induced pluripotent stem cells. Stem Cell Res Ther *5*: 58, 2014.
55 Cao L, Bombard J, Cintron K, Sheedy J, Weetall ML and Davis TW: BMI1 as a novel target for drug discovery in cancer. J Cell Biochem *112*: 2729-2741, 2011.
56 Moon JH, Heo JS, Kim JS, Jun EK, Lee JH, Kim A, Kim J, Whang KY, Kang YK, Yeo S, Lim HJ, Han DW, Kim DW, Oh S, Yoon BS, Scholer HR and You S: Reprogramming fibroblasts into induced pluripotent stem cells with Bmi1. Cell Res *21*: 1305-1315, 2011.
57 Villasante A, Piazzolla D, Li H, Gomez-Lopez G, Djabali M and Serrano M: Epigenetic regulation of Nanog expression by Ezh2 in pluripotent stem cells. Cell Cycle *10*: 1488-1498, 2011.
58 Ding X, Wang X, Sontag S, Qin J, Wanek P, Lin Q and Zenke M: The polycomb protein Ezh2 impacts on induced pluripotent stem cell generation. Stem Cells Dev *23*: 931-940, 2014.
59 Xie B, Zhang H, Wei R, Li Q, Weng X, Kong Q and Liu Z: Histone H3 lysine 27 trimethylation acts as an epigenetic barrier in porcine nuclear reprogramming. Reproduction *151*: 9-16, 2016.
60 Yi L, Lu C, Hu W, Sun Y and Levine AJ: Multiple roles of p53-related pathways in somatic cell reprogramming and stem cell differentiation. Cancer Res *72*: 5635-5645, 2012.
61 Ichida JK, Tcw J, Williams LA, Carter AC, Shi Y, Moura MT, Ziller M, Singh S, Amabile G, Bock C, Umezawa A, Rubin LL, Bradner JE, Akutsu H, Meissner A and Eggan K: Notch inhibition allows oncogene-independent generation of iPS cells. Nat Chem Biol *10*: 632-639, 2014.
62 Rasmussen MA, Holst B, Tumer Z, Johnsen MG, Zhou S, Stummann TC, Hyttel P and Clausen C: Transient p53 suppression increases reprogramming of human fibroblasts without affecting apoptosis and DNA damage. Stem Cell Rep *3*: 404-413, 2014.
63 Ron-Bigger S, Bar-Nur O, Isaac S, Bocker M, Lyko F and Eden A: Aberrant epigenetic silencing of tumor suppressor genes is reversed by direct reprogramming. Stem Cells *28*: 1349-1354, 2010.
64 Hou P, Li Y, Zhang X, Liu C, Guan J, Li H, Zhao T, Ye J, Yang W, Liu K, Ge J, Xu J, Zhang Q, Zhao Y and Deng H: Pluripotent stem cells induced from mouse somatic cells by small-molecule compounds. Science *341*: 651-654, 2013.
65 Kimura T, Kaga Y, Sekita Y, Fujikawa K, Nakatani T, Odamoto M, Funaki S, Ikawa M, Abe K and Nakano T: Pluripotent stem cells derived from mouse primordial germ cells by small molecule compounds. Stem Cells *33*: 45-55, 2015.
66 Lin T and Wu S: Reprogramming with Small Molecules instead of Exogenous Transcription Factors. Stem Cells Int *2015*: 794632, 2015.
67 Ruiz S, Diep D, Gore A, Panopoulos AD, Montserrat N, Plongthongkum N, Kumar S, Fung HL, Giorgetti A, Bilic J, Batchelder EM, Zaehres H, Kan NG, Scholer HR, Mercola M, Zhang K and Izpisua Belmonte JC: Identification of a specific reprogramming-associated epigenetic signature in human induced pluripotent stem cells. Proc Natl Acad Sci USA *109*: 16196-16201, 2012.
68 Bar-Nur O, Russ HA, Efrat S and Benvenisty N: Epigenetic memory and preferential lineage-specific differentiation in induced pluripotent stem cells derived from human pancreatic islet beta cells. Cell Stem Cell *9*: 17-23, 2011.
69 Buganim Y, Faddah DA and Jaenisch R: Mechanisms and models of somatic cell reprogramming. Nat Rev Genet *14*: 427-439, 2013.
70 Rais Y, Zviran A, Geula S, Gafni O, Chomsky E, Viukov S, Mansour AA, Caspi I, Krupalnik V, Zerbib M, Maza I, Mor N, Baran D, Weinberger L, Jaitin DA, Lara-Astiaso D, Blecher-Gonen R, Shipony Z, Mukamel Z, Hagai T, Gilad S, Amann-Zalcenstein D, Tanay A, Amit I, Novershtern N and Hanna JH: Deterministic direct reprogramming of somatic cells to pluripotency. Nature *502*: 65-70, 2013.
71 Vidal SE, Amlani B, Chen T, Tsirigos A and Stadtfeld M: Combinatorial modulation of signaling pathways reveals cell-type-specific requirements for highly efficient and synchronous iPSC reprogramming. Stem Cell Rep *3*: 574-584, 2014.
72 Xu XH and Zhong Z: Disease modeling and drug screening for neurological diseases using human induced pluripotent stem cells. Acta Pharmacol Sin *34*: 755-764, 2013.
73 Drawnel FM, Boccardo S, Prummer M, Delobel F, Graff A, Weber M, Gerard R, Badi L, Kam-Thong T, Bu L, Jiang X, Hoflack JC, Kiialainen A, Jeworutzki E, Aoyama N, Carlson C, Burcin M, Gromo G, Boehringer M, Stahlberg H, Hall BJ, Magnone MC, Kolaja K, Chien KR, Bailly J and Iacone R: Disease modeling and phenotypic drug screening for diabetic cardiomyopathy using human induced pluripotent stem cells. Cell Rep *9*: 810-821, 2014.
74 Musunuru K: Genome editing of human pluripotent stem cells to generate human cellular disease models. Dis Model Mech *6*: 896-904, 2013.
75 Chandrasekaran AP, Song M and Ramakrishna S: Genome editing: a robust technology for human stem cells. Cell Mol Life Sci, 2017. doi: 10.1007/s00018-017-2522-0. [Epub ahead of print]
76 Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, Cassady JP, Beard C, Brambrink T, Wu LC, Townes TM and Jaenisch R: Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. Science *318*: 1920-1923, 2007.
77 Doulatov S, Vo LT, Chou SS, Kim PG, Arora N, Li H, Hadland BK, Bernstein ID, Collins JJ, Zon LI and Daley GQ: Induction of multipotential hematopoietic progenitors from human pluripotent stem cells *via* respecification of lineage-restricted precursors. Cell Stem Cell *13*: 459-470, 2013.
78 Salci KR, Lee JH, Laronde S, Dingwall S, Kushwah R, Fiebig-Comyn A, Leber B, Foley R, Dal Cin A and Bhatia M: Cellular reprogramming allows generation of autologous hematopoietic progenitors from AML patients that are devoid of patient-specific genomic aberrations. Stem Cells *33*: 1839-1849, 2015.
79 Dutta D, Heo I and Clevers H: Disease modeling in stem cell-derived 3D organoid systems. Trends Mol Med *23*: 393-410, 2017.
80 Lee DF, Su J, Kim HS, Chang B, Papatsenko D, Zhao R, Yuan Y, Gingold J, Xia W, Darr H, Mirzayans R, Hung MC, Schaniel C and Lemischka IR: Modeling familial cancer with induced pluripotent stem cells. Cell *161*: 240-254, 2015.

81 Kuo KK, Lee KT, Chen KK, Yang YH, Lin YC, Tsai MH, Wuputra K, Lee YL, Ku CC, Miyoshi H, Nakamura Y, Saito S, Wu CC, Chai CY, Eckner R, Steve Lin CL, Wang SS, Wu DC, Lin CS and Yokoyama KK: Positive feedback loop of OCT4 and c-JUN expedites cancer stemness in liver cancer. Stem Cells *34*: 2613-2624, 2016.

82 Bernhardt M, Novak D, Assenov Y, Orouji E, Knappe N, Weina K, Reith M, Larribere L, Gebhardt C, Plass C, Umansky V and Utikal J: Melanoma-derived iPCCs show differential tumorigenicity and therapy response. Stem Cell Rep *8*: 1379-1391, 2017.

83 Nagai K, Ishii H, Miyoshi N, Hoshino H, Saito T, Sato T, Tomimaru Y, Kobayashi S, Nagano H, Sekimoto M, Doki Y and Mori M: Long-term culture following ES-like gene-induced reprogramming elicits an aggressive phenotype in mutated cholangiocellular carcinoma cells. Biochem Biophys Res Commun *395*: 258-263, 2010.

84 Komura S, Semi K, Itakura F, Shibata H, Ohno T, Hotta A, Woltjen K, Yamamoto T, Akiyama H and Yamada Y: An EWS-FLI1-induced osteosarcoma model unveiled a crucial role of impaired osteogenic differentiation on osteosarcoma development. Stem Cell Rep *6*: 592-606, 2016.

85 Chiou SS, Wang SS, Wu DC, Lin YC, Kao LP, Kuo KK, Wu CC, Chai CY, Lin CL, Lee CY, Liao YM, Wuputra K, Yang YH, Wang SW, Ku CC, Nakamura Y, Saito S, Hasegawa H, Yamaguchi N, Miyoshi H, Lin CS, Eckner R and Yokoyama KK: Control of oxidative stress and generation of induced pluripotent stem cell-like cells by JUN dimerization protein 2. Cancers *5*: 959-984, 2013.

86 Hoshino H, Nagano H, Haraguchi N, Nishikawa S, Tomokuni A, Kano Y, Fukusumi T, Saito T, Ozaki M, Sakai D, Satoh T, Eguchi H, Sekimoto M, Doki Y, Mori M and Ishii H: Hypoxia and TP53 deficiency for induced pluripotent stem cell-like properties in gastrointestinal cancer. Int J Oncol *40*: 1423-1430, 2012.

87 Izgi K, Canatan H and Iskender B: Current status in cancer cell reprogramming and its clinical implications. J Cancer Res Clin Oncol *143*: 371-383, 2017.

Received May 19, 2017
Revised May 29, 2017
Accepted June 2, 2017