STEM CELLS TRANSLATIONAL MEDICINE®

STANDARDS, POLICIES, PROTOCOLS, AND REGULATIONS FOR CELL-BASED THERAPIES

First Proposal of Minimum Information About a Cellular Assay for Regenerative Medicine

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Key Words. Stem cells • Information sharing • Biological specimen banks • Standards • Regenerative medicine • Quality control

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ABSTRACT

Advances in stem cell research have triggered scores of studies in regenerative medicine in a large number of institutions and companies around the world. However, reproducibility and data exchange among laboratories or cell banks are constrained by the lack of a standardized format for experiments. To enhance information flow in stem cell and derivative cell research, here we propose a minimum information standard to describe cellular assay data to facilitate practical regenerative medicine. Based on the existing Minimum Information About a Cellular Assay, we developed Minimum Information About a Cellular Assay for Regenerative Medicine (MIACARM), which allows for the description of advanced cellular experiments with defined taxonomy of human cell types. By using controlled terms, such as ontologies, MIACARM will provide a platform for cellular assay data exchange among cell banks or registries that have been established at more than 20 sites in the world. STEM CELLS TRANSLATIONAL MEDICINE *2016;5:1345–1361*

SIGNIFICANCE

Currently, there are more than 20 human cell information storage sites around the world. However, reproducibility and data exchange among different laboratories or cell information providers are usually inadequate or nonexistent because of the lack of a standardized format for experiments. This study, which is the fruit of collaborative work by scientists at stem cell banks and cellular information registries worldwide, including those in the U.S., the U.K., Europe, and Japan, proposes new minimum information guidelines, Minimum Information About a Cellular Assay for Regenerative Medicine (MIACARM), for cellular assay data deposition. MIACARM is intended to promote data exchange and facilitation of practical regenerative medicine.

INTRODUCTION

The invention of human embryonic stem (hES) cells in 1998 [1], followed by human induced pluripotent stem (hiPS) cells in 2007 [2], have spearheaded new developments in regenerative medicine around the world. A number of large-scale initiatives have been funded to make research- and clinical-grade hES and hiPS cell resources widely available to the global community [3]. Before clinical application, however, quality checks must be carried out to prove that artificially generated pluripotent stem cells and their differentiated cells can be used to form the basis for safe and effective cell therapies. To control the quality of engineered cells, assay data must be comparable to those of naturally existing cells in a defined format.

The data accumulation or exchange format must be capable of handling advanced experimental techniques with higher resolutions. Recently, next-generation sequencing techniques, in addition to use in the analysis of genome variation and the presence of virus sequences, are being applied to transcriptome and methylome analyses. In addition, cellular assays often demand single-cell resolution for quality checks. Indeed, it has been reported that, even in cells extracted from a single colony, the derivative cultures may remain heterogeneous, which may well have an impact on cell fate [4–7].

The accumulation of cellular assay data from pluripotent stem cells and their derivatives has already begun in iPS or embryonic stem (ES) cell banks and registries around the world. Cellular information gathered by cell banks is available to the general public. In contrast, cell registries collect cellular information from cell banks or laboratories and provide digital information through retrieval systems. Fifteen well-known stem cell banks and registries are listed in Table 1. The largest numbers of reported hES or hiPS cells for normal and diseased cells are 1,229 at the Human Induced Pluripotent Stem Cells Initiative (HipSci, http://www.hipsci.org) in the U.K.

Table 1. Examples of stem cell banks and registries (as of October 14, 2015)

Country	Bank or registry	Stem cell bank or registry	No. of hES/hiPSC entries	Website
EU	B	BLCB	Normal: 33	http://www.cmrb.eu/banco-lineas-celulares
	R	hPSCreg	Normal: 730	http://hpscreg.eu
			Diseased: 58	
U.K.	R	HipSci	Normal: 1229	http://www.hipsci.org
			Diseased: 207	
	B	U.K. Stem Cell Bank	Normal: 23 (approved research grade: 100; approved clinical grade: 41)	http://www.nibsc.org
			Diseased: 1	
	B	EBiSC	TBA	http://www.ebisc.org
U.S.	R	CIRM	Normal: 48	https://www.cirm.ca.gov/
	B	Coriell Institute	Diseased: 300	https://catalog.coriell.org/1/Stem-Cells
	B	Harvard Stem Cell Institute	Normal: 23	http://stemcelldistribution.harvard.edu
			Diseased: 3	
			Status unknown: 29	
	R	NIH Stem Cell Database	Normal: 21	https://stemcelldb.nih.gov/public.do
	B	NYSCF	Normal: 73	http://nyscf.org
			Diseased: 113	
	R	UMass ISCR	Normal: 1135	http://www.iscr-admin.com
			Diseased: 373	
			Abnormal karyotype: 65	
			Status unknown: 12	
	B	RUCDR Infinite Biologics	Normal: 25	http://www.rucdr.org
		NIMH Stem Cell Center	Diseased: 332	https://www.nimhgenetics.org/stem_cells
		NINDS Human Cell and Data Repository		https://bioq.nindsgenetics.org
		NIH CRM iPSC Collection		http://www.nimhgenetics.org/stem_cells/crm_lines.php
		Target ALS Foundation		http://www.targetals.org
	B	WiCell Research Institute	Normal: 69	http://www.wicell.org
			Diseased: 2	
JP	B	RIKEN BRC Cell Bank	Normal: 16	http://cell.brc.riken.jp/en
			Diseased: 320	
	R	SKIP	Normal: 137	http://www.skip.med.keio.ac.jp/en
			Diseased: 367	
			Status unknown: 152	
			Others: 6	

Abbreviations: ALS, amyotrophic lateral sclerosis; B, bank; BLCB, Stem Cell Bank of Barcelona; BRC, BioResource Center; CIRM, California Institute for Regenerative Medicine; CRM, Center for Regenerative Medicine; EBiSC, European Bank for Induced Pluripotent Stem Cells; EU, European Union; hES, human embryonic stem; hiPSC, human induced pluripotent stem cell; HipSci, Human Induced Pluripotent Stem Cells Initiative; hPSCreg, Human Pluripotent Stem Cell Registry; iPSC, induced pluripotent stem cell; JP, Japan; NIMH, National Institute of Mental Health; NINDS, National Institute of Neurological Disorders and Stroke; NYSCF, New York Stem Cell Foundation; R, registry; RUCDR, Rutgers University Cell and DNA Repository Infinite Biologics; SKIP, Stemcell Knowledge and Information Portal; TBA, to be announced; UMass ISCR, University of Massachusetts International Stem Cell Registry.

and 373 at the International Stem Cell Registry of University of Massachusetts Medical School in the U.S. (http://www.iscr-admin.com), respectively.

However, reproducibility and data exchange among cell banks or laboratories are compromised because of the lack of a standardized format for experiments. In order to exchange or integrate cellular assay information produced at different sites, not only measurement data, but also the format of additional experimental metadata, such as experimental design, sample information, measurement techniques, measurement uncertainty, etc.,

must be registered and rendered retrievable. The more metadata that are collected, the more precisely cellular assay experiments that are reproduced. However, this approach will generate a complex and redundant format, as well as require much space and time for curation. For the efficient collection of necessary information, it is vital to clarify minimum, yet indispensable, items for structuring the data format by which cellular assay data can be efficiently stored.

To solve this problem, Minimum Information (MI) Standards were invented as reporting guidelines for standardizing data entities. The first of such guidelines, Minimum Information About a Microarray Experiment, was organized by international consortia and established to integrate microarray data from various platforms [8]. It was followed by the Minimum Information About a Biomedical or Biological Investigation project in 2008 [9], which yielded approximately 80 MIs for various kinds of biological assays. Because those guidelines usually target simple phenomena in biological systems, several MIs may have to be combined to function as guidelines for holistic descriptions of cellular systems.

As the first attempt to enhance exchangeability of cellular assay data, Minimum Information About a Cellular Assay (MIACA) was created in 2008 as a reporting format that mainly focused on describing functional research using cell lines [10]. However, it was not designed to describe human somatic cells or advanced technologies for single-cell analysis. Moreover, for it to be applicable to regenerative medicine, experimental items must comply with existing drug and medical regulations. By reorganizing and extending MIACA, we developed Minimum Information About a Cellular Assay for Regenerative Medicine (MIACARM), which would allow for the description of advanced cellular experiments with defined taxonomy of human cell types.

In Figure 1, a conceptual view of how MIACARM contributes to stem cell research is shown. Our aim is to provide information of assays and data of all source cell types (somatic and engineered cells) at the clinical level, by which regenerative medicine and drug discovery can be conducted efficiently. In regenerative medicine research, there exists Minimal Information About T Cell Assays [11] for cell therapy and Bone/Cartilage Tissue Engineering Ontology [12] for tissue engineering, whereas in drug discovery, there exists Minimum Information required for a Drug Metabolizing Enzymes and Transporters Experiment [13] and Minimum Information About a Bioactive Entity [14]. However, important prerequisite information is lacking in these MIs, including how source cells, such as stem or differentiated cells, are generated by in vitro reprogramming or (trans)differentiation methods, as well as detailed characteristics of the source cells. In cases where the information does exist, it is described in free-text format. Recently, many research groups have been working on creating organoids for disease modeling, drug screening, and damaged tissue repair [15]. However, organoids present variability in their qualities, and, therefore, it is critical to check the detailed characteristics of the source cells. MIACARM plays an important role in ensuring that all safety and efficacy information is available for actual medical situations by providing a list of items to exclude ambiguously described assays and clarify data for cellular quality and safety evaluation.

By using controlled terms, such as ontologies, MIACARM can provide a platform for cellular assay data exchange among cell banks, registries, or databases that have been established at more than 20 laboratories or institutes around the world (Kurtz et al., manuscript in preparation). The first call for MIACARM was made at the 2014 Mainz Symposium, "Cell-Focused Data: Integration, Organization and Applications," and the present paper contains the first proposal to establish such a system. We expect that continuous international efforts will result in the further improvement of MIACARM.

Materials and Methods

Two Levels and Four Layers in MIACARM

We developed two levels of guidelines, MIACARM-I and -II. MIACARM-I is the guideline for omics assays in basic research using human cells; MIACARM-II is the guideline for practical regenerative medicine. Each guideline consists of a four-layered structure: modules, sections, subsections, and items, from top to bottom. Both guidelines will basically contribute to the exchange, maintenance, and reproducibility of cellular assay data.

Development of MIACARM Based on MIACA: Five Modules and 15 Sections

We first reorganized the existing cellular assay guideline, MIACA [10], and then developed a five-module structure consisting of Project, Source Cell, Assay, Experimental Technology, and Data (Fig. 2) as the top layer, based on the structure design of the Gene Expression Omnibus (GEO) database [16], which consists of three modules: Series, Sample, and Platform. We further divided Series of GEO into Project and Assay, and Sample of GEO into Source Cell and Data, to describe both the experimental protocols and information of the cells in greater detail in MIACARM. MIACARM consists of 257 items, which are summarized and categorized in supplemental online Table 1. As an extension of the MIACA structure, we also added four new sections to the source cell module to MIACARM.

In MIACARM-I, we added subsections for Sequencing and Marker Imaging Technology, which are absent in MIACA, to the Experimental Technology module to enable the description of current cell analysis devices. We also added two subsections to the Source Cell module, Cell Taxonomy and Anatomical Location. In MIACARM-II, we further added two more sections, Stem Cell Production and Stem Cell Quality Control, to the Source Cell module, according to two publications on stem cell banking [17, 18] and four regulations for products from (stem) cells or tissues in Japan, the U.S., and Europe [19–22]. To describe a single assay, a set of four modules—Assay, Source Cell, Experimental Technology, and Data—are required for reproducibility. Therefore, a single project module may contain one or more sets of the four modules to register multiple assays.

Ontology Assignment

To control proper curation terms in MIACARM, we collected and assigned necessary IDs and technical and ontological terms from 13 existing collections: BioAssay Ontology [23]; Cell: Expression, Localization, Development, Anatomy [24]; Chemical Entities of Biological Interest Ontology [25]; Cell Ontology [26]; EDAM Bioinformatics Operations, Data Types, Formats, Identifiers, and Topics [27]; Experimental Factor Ontology [28]; Biological Imaging Methods Ontology [29]; Foundational Model of Anatomy [30]; Medical Subject Headings [31]; Microarray and Gene Expression Data Ontology [32]; National Cancer Institute Thesaurus [33]; Ontology for Biomedical Investigations [34]; Uber Anatomy Ontology [35]; and PubMed/MEDLINE [36].

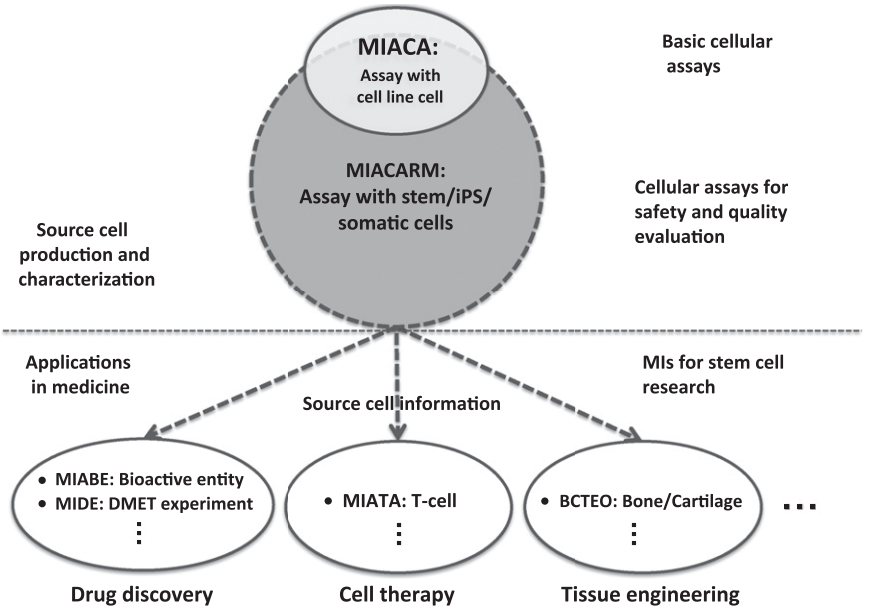

Figure 1. MIACARM enhances quality of stem cell research. In practical medicine, such as drug discovery, cell therapy, tissue engineering, etc., based on stem cells or their derivatives, MIACARM provides a procedure for source cell production and source cell quality and safety information to existing MIs. Abbreviations: BCTEO, Bone/Cartilage Tissue Engineering Ontology; DMET, Drug Metabolizing Enzymes and Transporters; iPS, induced pluripotent stem; MI, minimum information; MIABE, Minimum Information About a Bioactive Entity; MIACA, Minimum Information About a Cellular Assay; MIACARM, Minimum Information About a Cellular Assay for Regenerative Medicine; MIATA, Minimal Information About T Cell Assays; MIDE, Minimum Information Required for a Drug Metabolizing Enzymes and Transporters Experiment.

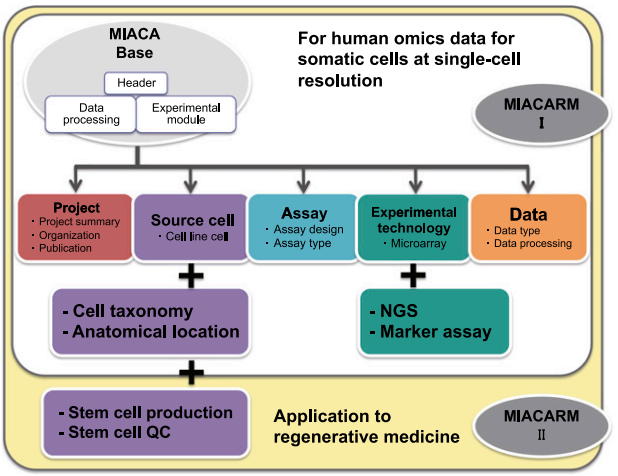

Figure 2. Basic structure of MIACARM: five modules and two levels (I and II). By reorganizing the three-module structure of MIACA, we adopted a five-module structure in MIACARM. MIACARM-I contains the guideline for basic research, which includes omics assays using human cells. MIACARM-II contains the guideline for practical regenerative medicine, which includes terms related to cell quality checks. Abbreviations: MIACA, Minimum Information About a Cellular Assay; MIACARM, Minimum Information About a Cellular Assay for Regenerative Medicine; NGS, next-generation sequencing; QC, quality control.

The assignment of those IDs and terms to the five modules and sections is summarized in supplemental online Table 1.

Evaluation of MIACARM

To evaluate how MIACARM reflects a realistic situation, we checked for overlapping items in two sections of MIACARM-II, Stem Cell Production and Stem Cell Quality Control, with the web items used by the 11 stem cell banks and registries listed in Table 1: Stem Cell Bank of Barcelona and Human Pluripotent Stem Cell Registry in the European Union; HipSci, and U.K. Stem Cell Bank in the U.K.; California Institute for Regenerative Medicine, the New York Stem Cell Foundation, the University of Massachusetts International Stem Cell Registry, Rutgers University Cell and DNA Repository Infinite Biologics, and WiCell in the U.S.; and Stemcell Knowledge and Information Portal and RIKEN BioResource Center in Japan. Descriptive items for cellular information provided by each website were collected, and unique terms were computationally selected by using the XML library in R statistical language (https://www.r-project.org).

Results

Enhancement of Data Exchange and Comparability Among Different Assays by MIACARM

MIACARM is designed to exchange assay information among different experimental techniques. In particular, the new five-module structure makes it easier to understand assays at the level of materials and methods than does the three-module structure in MIACA. As shown in Figure 3, we separate Reagent, Instrument, and Cell Line from the subsection (Bio) Materials in the Header module of MIACA and combine them with the Experimental Modules of MIACA to generate the new Experimental Technology module in MIACARM. By this reorganization, material information and method information become independent, and any experimental combination of Source Cell and Experimental Technology can be produced, which enhances understanding of the whole experimental process. Similarly, the

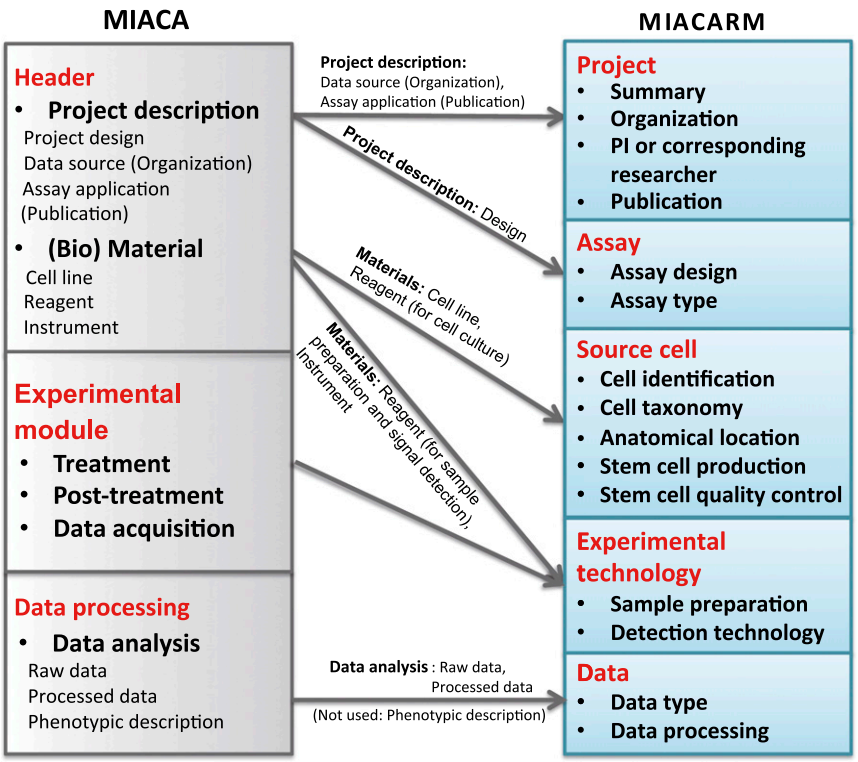

Figure 3. Differences in modules and sections between MIACA and MIACARM. In contrast to the three-module structure in MIACA, a five-module structure in MIACARM was developed to enhance the understanding of assays at the materials and methods level. Abbreviations: MIACA, Minimum Information About a Cellular Assay; MIACARM, Minimum Information About a Cellular Assay for Regenerative Medicine; PI, principal investigator.

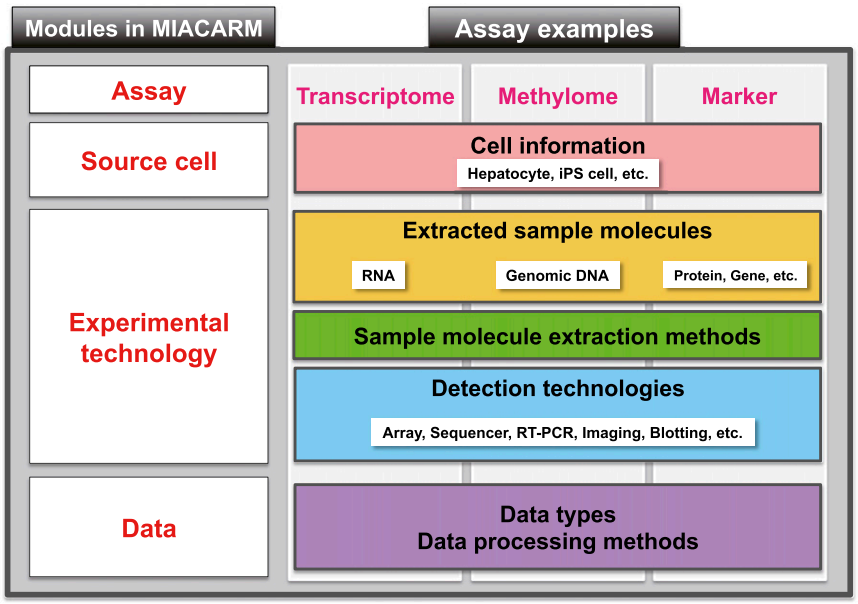

Figure 4. Example of exchangeability and comparability of transcriptome, methylome, and marker assays. The five-module structure (Project module is not shown) makes it easy to search for various combinations of cell materials and experimental methods. Abbreviations: iPS, induced pluripotent stem; MIACARM, Minimum Information About a Cellular Assay for Regenerative Medicine; RT-PCR, reverse-transcription polymerase chain reaction.

Project Description section in the Header module of MIACA is separated at the subsection level into the Project and Assay modules of MIACARM. This reorganization is especially important when retrieving assays from a database. For example, when searching for assays that use microarray technology, array experiment-specific information, such as experimental conditions, reagents, and instruments, can be found in the single Experimental Technology module in MIACARM, whereas those

would have to be retrieved from both the Header and Experimental Modules in MIACA. Figure 4 shows how experiments such as transcriptome, methylome, and marker assays are exchangeable and comparable. Overall, the new five-module structure is user-oriented, because it makes searching for assays consisting of various combinations of source cells and experimental methods easy.

MIACARM-II: Minimum Information for Stem Cell Research

Various cell banks that generate and establish stem cell lines have been launched worldwide. Cell registries that accumulate digital information from those cell banks have been established as well (Table 1). However, major issues regarding the workability of the cell banks exist and are as follows: (a) there has been no consensus on the quality evaluation of artificially generated stem cells [17, 18], and, thus, (b) no standardized method is available for establishing the highest-quality stem cells [37, 38]. A method for checking whether the established stem cells are of research or clinical grade is still under discussion, although an international consensus on key issues for the establishment of human pluripotent stem cell banks has been published [39]. Even more problematic is the fact that there are no minimum information standards for describing the qualitative or quantitative characteristics of established stem cells [40, 41], which hampers comparisons between cell lines established in different banks or laboratories.

Considering this situation, we first collected items to describe the production procedures and quality checks of stem cells for the "Source cell" module on the basis of six documents for the proper management of cells [17–22] (Materials and Methods). Among those items, we selected 144 items that are required to assess product quality, safety, and efficacy, as indicated by the international guidelines for medicines established in Japan, the U.S., and Europe [42]. Table 2 shows the list of necessary items selected, reference numbers, adoption status by stem cell banks and registries, and MIACARM levels. The items are divided into five categories: (a) produced stem cell summary, (b) ethical operation, (c) material, (d) cell banking process, and (e) cell characterization and sterility testing.

Upon checking whether each of the 144 items is adopted by the 11 stem cell banks and registries, we found that sterility testing is adopted by most of the stem cell banks and registries. However, many items considered important in practical medicine, such as human leukocyte antigen type, single nucleotide polymorphism (SNP), tumorigenesis, etc., are not open to the general public, probably because of privacy issues. Furthermore, information required for regulatory compliance for manufacture of regenerative medicines, such as source cell information, culture conditions, culture protocol, etc., are generally missing. Importantly, we also found four items necessary for stem cell information registration in which the reference is missing (Table 2). Those four items are stem cell ID, date (stem cells) placed in storage, subjected ethical approvals and accrediting agencies involved, and reprogramming type in the stem cell establishment process. From the biobanking and repository perspective, it is critically important to use widely available short tandem repeat (STR) or SNPTrace assays to unambiguously document the identity of each biospecimen (source cell, hiPS cells, differentiated cell lines, etc.) to address potential sample mislabeling or swaps that can occur during sample collection and processing [43]. Instances of such errors, which can have profound and costly adverse effects on research studies, are well documented [44].

Validating Items in MIACARM-II As Minimum Information

To evaluate the selected minimum items in MIACARM-II, each item in Table 2 is scored by counting the numbers of source references and stem cell banks that adopted it. The results are shown in Figure 5. Red lines indicate an arbitrary 20% threshold of acceptance of items by either source references or stem cell banks, and the four areas separated by the two lines are labeled I–IV clockwise from the top left. The numbers of items in areas I–IV are 18, 50, 75, and 1, respectively. When we examined the independences of the item distributions by Pearson's χ^2 test with Yates' continuity correction using chisq.test function in statistical computing language R, we found a probability of 2.6×10^{-5} that was significantly low, and the probabilities of the standardized residuals for all areas were also significant (i.e., areas I and III contain larger numbers of items, and areas II and IV contain smaller numbers of items). In area II, the items that received high scores from both source references and stem cell banks are important in many fields of stem cell research and application. Items in area I received high scores from stem cell banks and included attributes associated with stem cell materials, such as Stem Cell Name, Contact Information of Provider/Distributor (Distribution Bank), and biological information of source cell donor, such as Gender of Donor, Age of Donor When Source Cell Was Obtained, and Informed Consent From Donor. In particular, all six items with high scores in box "a" are used for database management rather than for describing the safety or quality of the materials, including Stem Cell ID, Stem Cell Name, Contact Information of Generator, and Provider/Distributor (Distribution Bank). It is noteworthy that most items are distributed in area III, where high scores are received from source references, and are mainly about experimental materials used in the stem cell culture and establishment. The three items in box b, which received the highest scores from source references, comprise two items, Basal Medium and Culture Additive and Concentration, related to the culture conditions of the source cells, and, more important, one item, Copy Number Variation (CNV), which cannot be provided from the raw data provided by stem cell banks because of privacy issues. Only HipSci provides sanitized CNV data by scatter plot. Finally, in area IV, which is the least supported by source references and stem cell banks, we observed only one item, Single Nucleotide Polymorphisms (SNPs), in MIACARM that considers cancer risks [45, 46] as safety information for stem cells used as clinical products.

Discussion

We propose for the first time a minimum information standard to describe cellular assay data for the facilitation of practical regenerative medicine. This proposal was made on the basis of the presentations delivered at the 2014 Mainz Symposium, "Cell-Focused Data: Integration, Organization and Applications," and serves as a starting point for promoting international contributions toward its further development. Based upon the existing MIACA, we developed MIACARM, which is expected

Table 2. Checklist for stem cell production and QC items in the Source Cell module in MIACARM-II

		Stem cell bank and registry											
		EU		U.K		U.S.					JP		
Item	Source documents	BLCB	hPSCreg	HipSci	U.K. SCB	CIRM	NYSCF	UMass ISCR	RUCDR	WiCell	SKIP	RIKEN BRC	Covered by MIACARM
Stem cell production													
Produced stem cell summary													
Stem cell general IDs													
Stem cell ID	—[a]		○		○	○	○		○	○	○	○	II
Stem cell name	[17]	○	○	○	○			○	○	○	○	○	II
Lot no.	[19, 20]							○	○	○		○	II
Cell grade	[17]				○			○		○	○		II
Passage number	[17–20]	○	○		○			○	○	○			II
Date placed in storage	—[a]	○			○				○	○			II
Produced by (generator, institution name)	[18]	○	○		○	○	○	○	○	○	○	○	II
Contact information of generator	[18]	○	○		○	○	○	○	○	○	○	○	II
Provider/distributor (distribution bank)	[17]		○	○	○	○	○	○	○	○	○	○	II
Contact information of provider/distributor (distribution bank)	[17]		○			○	○		○		○		II
Reference publications	[17]	○	○		○			○	○		○		II
Ethical operation													
Informed consent from donor	[20]	○	○		○	○			○				II
Subjected to ethical approvals and accrediting authorities involved	—[a]	○	○		○	○			○				II
Material													
Donor ID													
Gender of donor	[20]		○	○			○	○	○	○	○	○	I
Age of donor when source cell was obtained	[20]		○	○			○		○		○	○	I
Race of donor	[17, 18]				○		○				○	○	I
Ethnological characteristic of donor	[19, 22]				○		○						II
Health/disease status of donor	[17–20]	○	○	○	○	○	○	○	○	○	○	○	I

Table 2. (*Cont'd*)

Item	Source documents	Stem cell bank and registry											Covered by MIACARM
		EU		U.K		U.S.					JP		
		BLCB	hPSCreg	HipSci	U.K. SCB	CIRM	NYSCF	UMass ISCR	RUCDR	WiCell	SKIP	RIKEN BRC	
Health/disease history of donor	[19, 20]					○			○				I
HLA type	[18–21]	○						○			○		II
STR or SNPTrace panel fingerprinting	[17–20]	○						○	○	○	○	○	II
Donor testing method conducted	[19, 20, 22]												II
Donor screening method conducted	[19, 20, 22]												II
Source cell ID													
Source cell type	[17–20]	○	○	○	○	○	○	○	○	○	○	○	I
Source cell description	[19, 20]			○	○				○	○	○	○	I
Organ/tissue from which source cell was obtained	[17–20]	○			○					○	○	○	I
Laboratory testing of source cell	[19, 20]								○				II
Source cell providing institution (master cell bank)	[19–22]			○					○				I
Source cell providing institution contact information	[19–22]												I
Materials used for culture of source cells													
Basal medium	[17–22]												II
Basal medium vendor and lot no.	[19–22]												II
Culture additive and concentration	[17–22]												II
Antibiotic name and concentration (if used)	[18–22]												II
Coating substrate name (if used)	[18–22]												II
Feeder cell name (if used)	[18–22]												II
Feeder cell seeding density (if used)	[19–22]												II

Table 2. (*Cont'd*)

Item	Source documents	Stem cell bank and registry											Covered by MIACARM
		EU		U.K		U.S.					JP		
		BLCB	hPSCreg	HipSci	U.K. SCB	CIRM	NYSCF	UMass ISCR	RUCDR	WiCell	SKIP	RIKEN BRC	
Feeder cell preparation protocol	[19–22]												II
Synthesized basement membrane name (if used)	[19–22]												II
Nanofiber name (if used)	[19–22]												II
Bead name (if used)	[19–22]												II
Other materials name (if used)	[19–22]												II
Safety and sterility descriptions of materials/agents used	[19–22]												II
Materials used for source cell procurement													
Source cell transferring container	[19, 20]												II
Source cell transferring media	[19, 20]												II
Source cell storage/ banking container	[19, 20]												II
Source cell storage/ banking media	[19, 20]												II
Source cell storage/ master cell banking protocol	[19, 20]												II
Material transferring container	[17–20]												II
Materials used for culture in stem cell establishment step													
Basal medium	[17–22]	○	○	○	○	○			○	○	○	○	II
Basal medium vendor and lot no.	[19–22]												II
Culture additive and concentration	[17–22]	○	○	○	○				○	○	○	○	II
Antibiotic name and concentration (if used)	[18–22]			○					○			○	II

Table 2. (*Cont'd*)

Item	Source documents	Stem cell bank and registry											Covered by MIACARM
		EU		U.K		U.S.					JP		
		BLCB	hPSCreg	HipSci	U.K. SCB	CIRM	NYSCF	UMass ISCR	RUCDR	WiCell	SKIP	RIKEN BRC	
Coating substrate name (if used)	[18–22]		○	○					○	○			II
Feeder cell name (if used)	[18–22]	○	○	○	○			○	○	○	○		II
Feeder cell seeding density (if used)	[19–22]										○		II
Feeder cell preparation protocol (if used)	[19–22]												II
Synthesized basement membrane name (if used)	[19–22]								○				II
Nanofiber name (if used)	[19–22]												II
Bead name (if used)	[19–22]												II
Names of other materials (if used)	[19–22]								○				II
Safety and sterility descriptions of materials/agents used	[19–22]												II
Materials used for culture in final step of stem cell production													
Basal medium	[19–22]		○	○	○					○		○	II
Basal medium vendor and lot no.	[19–22]												II
Culture additive and concentration	[19–22]		○	○	○					○		○	II
Antibiotic name and concentration (if used)	[19–22]			○								○	II
Coating substrate name (if used)	[19–22]		○							○			II
Feeder cell name (if used)	[19–22]		○	○	○			○		○			II
Feeder cell seeding density (if used)	[19–22]												II
Feeder cell preparation protocol	[19–22]												II

Table 2. (*Cont'd*)

Item	Source documents	Stem cell bank and registry											Covered by MIACARM
		EU		U.K		U.S.					JP		
		BLCB	hPSCreg	HipSci	U.K. SCB	CIRM	NYSCF	UMass ISCR	RUCDR	WiCell	SKIP	RIKEN BRC	
Synthesized basement membrane name (if used)	[19–22]												II
Nanofiber name (if used)	[19–22]												II
Bead name (if used)	[19–22]												II
Names of other materials (if used)	[19–22]												II
Safety and sterility descriptions of materials/agents used	[19–22]												II
Materials used for stem cell storage and transfer/ shipping													
Stem cell storage/ banking media	[19, 20, 22]								○				II
Stem cell storage/ banking container	[19, 20]								○				II
Stem cell transferring/ shipping media	[19, 20, 22]								○				II
Stem cell transferring/ shipping container (packing)	[19, 20]								○				II
Cell banking process													
Source cell procurement process													
Source cell procurement protocol	[19–21]					○			○				II
Source cell transferring container	[19–21]												II
Source cell transferring method	[19, 20]												II
Source cell transferring protocol	[19, 20]												II
Source cell storage/ banking media	[19, 20]								○				II
Source cell storage/ master cell banking method	[19, 20]												II

Table 2. (*Cont'd*)

Item	Source documents	Stem cell bank and registry											Covered by MIACARM
		EU		U.K		U.S.					JP		
		BLCB	hPSCreg	HipSci	U.K. SCB	CIRM	NYSCF	UMass ISCR	RUCDR	WiCell	SKIP	RIKEN BRC	
Source cell storage/ master cell banking protocol	[19, 20]												II
Material transferring method	[17–20]												II
Material transferring protocol	[17–20]												II
QC for source cell culture conditions													
Culture temperature	[17, 19]		○		○				○	○		○	II
% O_2 concentration in air	[17, 19]		○						○				II
% CO_2 concentration in air	[17–19]		○		○				○	○		○	II
Passage protocol	[17–19]								○	○		○	II
Stem cell establishment process													
Reprogramming type	—[a]	○	○	○		○	○	○	○				II
Transgene name and amount	[19–22]	○	○		○			○			○	○	II
Vector type	[19–22]		○	○			○	○	○		○	○	II
Virus type	[19–22]		○	○			○	○	○				II
Transgene induction method	[19–22]		○				○		○		○		II
Transgene induction efficiency	[19–22]												II
Protein name and amount	[19–22]												II
Protein induction method	[19–22]		○										II
Protein induction efficiency	[19–22]												II
Small molecule name and concentration	[19–22]												II
Small molecule induction method	[19–22]		○										II

Table 2. (*Cont'd*)

Item	Source documents	Stem cell bank and registry											Covered by MIACARM
		EU		U.K		U.S.					JP		
		BLCB	hPSCreg	HipSci	U.K. SCB	CIRM	NYSCF	UMass ISCR	RUCDR	WiCell	SKIP	RIKEN BRC	
Original provider of molecule	[19–22]												II
Procurement of molecule (molecule preparation method)	[19–22]												II
Establishment protocol (molecular induction protocol)	[19–22]		○	○									II
Cell population purity	[19, 21]		○										II
In-process control used	[19, 21, 22]												II
Intermediate product cell information (if existing)	[19–21]												II
QC for stem cell culture conditions													
Culture temperature	[17, 19]		○	○	○				○	○		○	II
% O_2 concentration in air	[17, 19]		○						○				II
% CO_2 concentration in air	[17–19]		○	○	○				○	○		○	II
Culture protocol	[19]	○	○	○					○				II
Passage protocol	[17–19]		○	○					○	○		○	II
QC for stem cell storage/ banking conditions													
Stem cell storage/ banking protocol	[17, 19–22]				○								II
Stem cell density for storage/banking	[17, 19–22]		○		○				○			○	II
Stem cell cryopreservation/ freezing method	[17, 19–22]		○		○				○			○	II
Stem cell cryopreservation/ cooling temperature	[17, 19–22]		○		○				○			○	II
Stem cell cryopreservation cryoprotectant	[17, 18]				○				○			○	II

Table 2. (*Cont'd*)

Item	Source documents	Stem cell bank and registry											Covered by MIACARM
		EU		U.K		U.S.					JP		
		BLCB	hPSCreg	HipSci	U.K. SCB	CIRM	NYSCF	UMass ISCR	RUCDR	WiCell	SKIP	RIKEN BRC	
Stem cell cryopreservation/ cooling rate	[18, 19]								○				II
Stem cell storage/ banking condition	[17, 19–22]								○				II
Stem cell QC													
Cell characterization and sterility testing													
Stem cell characteristics													
Population doublings	[17, 18, 20]											○	II
Crisis population doubling level	[18, 20]											○	II
Viability at thawing	[17–22]	○			○			○	○	○	○	○	II
Teratoma formation	[18–20]	○	○				○	○			○		II
Differentiation ability in vitro	[18–22]	○	○				○		○		○		II
Differentiation propensity	[18–22]		○					○					II
Tumorigenesis	[18–22]												II
Morphology	[17–22]	○	○		○				○		○	○	II
Cell image	[17]			○				○	○		○	○	II
Marker gene expression	[17–22]	○	○		○			○	○		○		II
Surface antigen expression	[19–22]							○	○			○	II
Karyotyping and used method	[17–22]	○	○		○			○	○	○	○	○	I
CNV	[17–22]												II
SNP	[18]										○		II
Residual exogene detection	[19–22]	○	○						○	○	○	○	II
Genome profiling	[18–22]	○	○	○	○						○		I
Transcriptome profiling	—[a]		○	○							○		I
Epigenome profiling	[18]	○	○	○							○		I

Table 2. (*Cont'd*)

Item	Source documents	Stem cell bank and registry											Covered by MIACARM
		EU		U.K		U.S.				JP			
		BLCB	hPSCreg	HipSci	U.K. SCB	CIRM	NYSCF	UMass ISCR	RUCDR	WiCell	SKIP	RIKEN BRC	
QC for sterility of stem cell													
Bacterial contamination (sterility test)	[17–22]	○	○		○					○		○	II
Fungal contamination (sterility test)	[17–22]	○	○		○					○		○	II
Mycoplasma contamination	[17–22]	○	○		○				○	○	○	○	II
Protozoal contamination	[17–22]		○		○			○		○		○	II
Viral contamination	[17, 19–22]												II
Other sterility test	[17, 22]		○		○			○					II

[a]Items appear in the listed 11 stem cell registries.

Abbreviations: BLCB, Stem Cell Bank of Barcelona; BRC, BioResource Center; CIRM, California Institute for Regenerative Medicine; CNV, copy number variation; HipSci, Induced Pluripotent Stem Cells Initiative; HLA, human leukocyte antigen; hPSCreg, European Human Pluripotent Stem Cell Registry; MIACARM, Minimum Information About a Cellular Assay for Regenerative Medicine; NYSCF, New York Stem Cell Foundation; QC, quality control; RUCDR, Rutgers University Cell and DNA Repository Infinite Biologics; SKIP, Stemcell Knowledge and Information Portal; SNP, single nucleotide polymorphism; STR, short tandem repeat; U.K. SCB, U.K. Stem Cell Bank; UMass ISCR, University of Massachusetts International Stem Cell Registry.

Figure 5. Evaluation of items in Minimum Information About a Cellular Assay for Regenerative Medicine II (MIACARM-II). Items in MIACARM-II are scored by counting the numbers of source references on the basis of data in Table 2. Red lines indicate 20% threshold of acceptance by either source references or stem cell banks.

to enable (a) the description of advanced cellular experiments with defined taxonomy of human cell types and controlled terms (MIACARM-I), and (b) the description of production procedures and quality checks of stem cells (MIACARM-II). MIACARM is expected to provide a platform for cellular assay data exchange among cell banks or registries around the world. Furthermore, we anticipate several important regulatory advantages by adopting MIACARM: (a) deposition of the minimum information and assay metadata to reduce missing and unnecessary information about the cells, (b) progress toward reproducible experiments, and (c) retrieval by omnibus search across all cell banks and registries in the world.

Related Efforts and Paths to Optimize Minimum Guidelines

Currently, there are more than 20 human cell information storage sites, such as banks, registries, and databases, in the world. However, reproducibility and data exchange among different laboratories or cell information storages are usually inadequate or nonexistent because of the lack of a standardized format for experiments. Moreover, the standardization of cell-quality evaluations in relation to regenerative medicine products is still under discussion. Despite the launch of the first clinical trial based on iPS cells in Japan in 2014 [47], subsequent actions following that study have been delayed, reflecting caution toward patient treatment. This delay is expected given the current lack of standards for cell preparation and assessment and little experience in stem cell therapies. MIACARM is expected to contribute to the development of comparative standards. Because MIACARM was developed on the basis of proposals and regulations in Japan, the U.S., and Europe—the three jurisdictions involved in development standards under the International Consensus on Harmonization—we expect it to mature and become a consensus guideline that reflects practice of and advances in regenerative medicine. Another effort for the standardization of stem cell

research is the development of stem cell and cell line nomenclature [40, 48–50]. Such nomenclature would be integrated into MIACARM as a unique cell type name descriptor, which would reduce errors and confusion about the cells used in any experiments. Recently, the draft "Guidelines for Stem Cell Science and Clinical Translation" was proposed by the International Society for Stem Cell Research [51]. However, this draft proposes guidelines toward establishing regulatory rules. Conversely, discussions with stem cell experts are needed to determine the items required for inclusion in MIACARM as "minimum" mandatory information and a framework drafting for standardization issues from cell banking to the manufactured regenerative medicine product proposed by Stacey (2014) [52]. To optimize MIACARM, we need to organize international conventions on a periodic basis that draw consensus from a broader range of experts involved in world stem cell bank registries. We should also bring MIACARM to the attention of the International Organization of Standardization, currently beginning to develop approaches to standards in regenerative medicine manufacturing, and the Organisation for Economic Co-operation and Development which is currently developing a new standard for good in vitro methodology.

Flexibility to Incorporate Newly Developed Techniques and Increasing Number of Cell Types

We have also developed a human cell repository database called SHOGoiN (formerly CELLPEDIA [53]), where we curate gene expression data in a defined format using the MIACARM guideline. Recently, more advanced experimental techniques at single-cell resolution, including transcriptome, methylome, proteome, etc., have been reported. For example, the single-cell mass cytometry assay can identify 18 types of hematopoietic cells on the basis of surface antigens [54]. To enter those data, MIACARM must have sufficient flexibility to incorporate newly developed techniques. In addition, unidentifiable or new cell types have been found by single-cell analysis [55]. Therefore, MIACARM must be sufficiently flexible to deal with the continuously increasing number of cell types. In the future, an extended MIACARM would be required for more precise description of other important cellular assays based on stem cells, such as disease modeling, drug discovery, tissue engineering, etc.

Conclusion

One important issue to be resolved is how to handle and store massive cell data. By using single-cell barcode technology, thousands of cells are analyzed at one time to measure omics data [56]. We expect to encounter millions of cell omics measurement data, from which we need to retrieve only necessary information for particular cell types. To resolve the massive cell data handling and storage issue, new computational systems, such as distributed or cloud-type databases, are proposed by bio-database sites in the world [57–59]. However, such distributed database systems require not only time and funding, but also an international cooperation by a large number of consenting researchers (Kurtz et al., manuscript in preparation). In any case, extended MIACARM or completely new cellular assay guidelines would be needed to support such systems in the coming big data era.

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Author Contributions

K.S.: conception and design, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; A.K., G.S., and M.S.: provision of study material or patients, final approval of manuscript; W.F.: conception and design, data analysis and interpretation, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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